MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

AIR QUALITY ADVISORY COMMITTEE

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ALSO PRESENT

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Patrick Temple, Ph.D

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PROCEEDINGS

CHAIRPERSON KLEINMAN: Good morning. I'd like to start this meeting of the Air Quality Advisory Committee. And my name is Mike Kleinman. I'm chairing the Committee today.

And the topic is going to be the proposed changes to nitrogen dioxide.

And just to remind everybody, when you're making your comments, use the microphone. It will help the stenographer get it.

And what I'd like to do is just go around the table and have the members of the Committee introduce themselves and their affiliations. And start with Russ.

ADVISORY COMMITTEE MEMBER SHERWIN: I'm Russell Sherwin from the University of Southern California, Department of Pathology. I'm a Professor of Pathology at the Keck School of Medicine.

ADVISORY COMMITTEE MEMBER ADAMS: Good morning. I'm Bill Adams, Professor Emeritus, from University of California at Davis. Now in my second year of retirement in Albuquerque. My grandson, eight years old, he's going to the same elementary school that I taught P.E. in from 1958 to '61.

(Laughter.)

ADVISORY COMMITTEE MEMBER ADAMS: The rest of

years I won't share with you. But pleasure to be here.

ADVISORY COMMITTEE MEMBER SHEPPARD: Dean Sheppard. I'm a Professor Medicine at University of California, San Francisco.

ADVISORY COMMITTEE MEMBER FANUCCHI: I'm Michell Fanucchi. I'm a Research Faculty in the School of Veterinary Medicine at UC Davis.

ADVISORY COMMITTEE MEMBER PLOPPER: Charles Plopper, Professor of Cell Biology, University of California at Davis.

ADVISORY COMMITTEE MEMBER CHESTNUT: I'm Lauraine Chestnut. I'm an economist with Stratus Consulting in Boulder, Colorado.

ADVISORY COMMITTEE MEMBER DELFINO: Ralph Delfino, Associate Professor, UC Irvine, in epidemiology.

ADVISORY COMMITTEE MEMBER PLATZKER: Arnold Platzker. I'm at Childrens Hospital in Los Angeles where I head the cystic fibrosis program. I'm Professor of Pediatrics at Keck School of Medicine, an adjunct professor at UCLA.

ADVISORY COMMITTEE MEMBER GREEN: Peter Green. I'm a research engineer in the Department of Civil and Environmental Engineering at UC Davis.

CHAIRPERSON KLEINMAN: Okay. And I'd like to turn it over to Richard Bode and continue.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Great. Thank you, Dr. Kleinman and members of the Committee. As he said, I'm Richard Bode. I'm Chief of the Health and Exposure Assessment Branch in the Air Resources Board. And our group is responsible for recommending changes to our air quality standards -- California's ambient air quality standards.

And our business at hand today is the review of the California ambient air quality standard for nitrogen dioxide. We have a technical support document that contains the findings of a staff review by the Air Resources Board and the Office of Environmental Health Hazard Assessment.

(Thereupon an overhead presentation was Presented as follows.)

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: First, kind of to -- actually to go off, that you should have in your packets -- or you should have gotten an agenda of today's meeting. We gave you copies of slides, I hope you got, both the beginning slides by the Air Resources Board staff and then by the Office of Environmental Health Hazard Assessment staff as well.

And I was going to say, for anybody from the public there's also slides in the room outside and also a sign-up sheet for the public to sign in.

Tomorrow morning if we keep to our schedule, see how our schedule's doing, we have a period for public comments for anybody in the public that wants to sign up for providing oral public comments. If they want to sign in, then we'll know about how many people we have. And that will help us adjust our schedule for tomorrow.

And with that, I think -- let's see. I've got basically sitting at the table today, and just to kind of introduce them, is Dr. Norman Kado, who's the lead for the Air Resources Board on the review of the nitrogen dioxide standard. Next to him is Dr. Bart Ostro, who is the -- I guess the lead for OEHHA, and Dr. Janice Kim as well.

I think -- we had -- in fact, Norm will get into this. But I thought I'd also introduce Dr. Francesco Forastiere, who's one of our consultants who came from -- all the way from Italy for our AQAC meeting. So very glad to have him today.

And is Pat Temple here?

And then we've got Dr. Temple -- oh, good.

And Dr. Patrick Temple, who also is one of our consultants.

Thank you for coming too.

And who helped us actually with the welfare section of our document.

So with that, I'm going to turn over actually the

staff presentation -- oops.

I was just reminded that Dr. Mark Frampton also was one of our consultants who helped write a good deal of the -- helped us write the report itself. Unfortunately couldn't make it today, was very busy. But I have it on authority, we have his cell phone number. So if we get hard questions, we can call him up.

Okay. Norm, would you get the next slide.

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ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: And I'm just going to kind of briefly review what we're going to do today in our two-day meeting. And this morning, if you'll look at your agenda too, this morning we're going to have some brief staff summaries that will basically -- both ARB and OEHHA staff will briefly review what's in our technical support document. And then OEHHA will discuss their recommendation for revisions to the NO2 standard, nitrogen dioxide standard. We'll follow that with -- basically that's the period for the Committee to do their peer review. We've broken it up by major sections, and comment on both the document and the basis for the recommendations.

And that should fill out our day today. And I'll say we'll have to check our schedule as we go and see if we're getting extra time.

And then tomorrow is planned for oral public comments followed by staff responses to both oral and written comments.

And we did pass out also for you responses to public comments that are in kind of a PowerPoint format there that I handed out this morning. We'll probably talk about those after.

And then at the end of the day tomorrow we'll have AQAC's findings. And Dr. Kleinman will probably lead that.

So are there any questions?

If not, I'll let Dr. Kado begin his staff presentation.

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DR. KADO: Thank you, Mr. Bode. Good morning, Dr. Kleinman and members of the Air Quality Advisory Committee.

My name is Norman Kado from the Air Resources Board, one of the leads for the nitrogen dioxide standard Richard has mentioned.

The staff presentation begins today with an overview of the standard setting in California, including a summary of the Children's Environmental Health Protection requirements, the regulatory process and the AQAC responsibilities.

I'll transition to a discussion of the staff review of the scientific literature. And Dr. Bart Ostro from OEHHA will present the health science review and then present OEHHA's recommendation for revising the nitrogen dioxide standard and the basis for that recommendation.

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DR. KADO: To begin, in California an ambient air quality standard is the legal definition of clean air. It has a number of elements including -- in the definition including the definition of the pollutant, in this case nitrogen dioxide, and averaging time, a concentration, a monitoring method, and the form of the standard such as "not to be exceeded".

California ambient air quality standards are based solely on public health considerations. They provide a basis for preventing or abating adverse health effects.

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DR. KADO: California standard setting does not include consideration of the following: Methods for attainment designation, the feasibility of controls, the cost of controls, or the implementation of controls.

The process for making attainment designations is specified in sections of the California Code of Regulations that are unrelated to those we have opened in

the present regulatory action and not involved in the regulatory action under consideration in this meeting.

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DR. KADO: To begin, why are we reviewing the State nitrogen dioxide standard? State law requires that ambient air quality standards protect public health and that they are to be periodically reviewed to ensure that they adequately protect public health.

Further, in 1999, the Children's Environmental Health Protection Act, or SB 25, was approved and requires the ambient air quality standards adequate to protect public health, with a particular emphasis on the health of infants and children.

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DR. KADO: In response to the children's Environmental Health Program, all California ambient air quality standards were reviewed. And the results of that review are contained in the report approved by the ARB in the year 2000. The conclustion was that many of the California ambient air quality standards might not adequately protect the health of the public including infants and children. The standards found possibly inadequate were then prioritized based on the extent of risk to public health. And the standards for particulate matter were of greatest concern, and full review of the

PM10 sulfate standard was completed in 2002, with the new standards becoming effective in 2003.

Ozone was the second greatest concern. And as a result the standard was fully reviewed, revised and approved by the Board in 2005, with the new standard becoming effective in May of 2006.

Nitrogen dioxide was the third in a series of pollutants that had the highest priority for its risk to the public health including children. This brings us to the current review of nitrogen dioxide.

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DR. KADO: The Federal Clean Air Act gives California authority to set its own ambient air quality standards in consideration of statewide concerns. Because the California ambient air quality standards are state regulations, federal laws pertaining to the process and procedures for setting standards do not apply. Instead we must follow the process and procedures outlined by the California Health and Safety Code and the California Administrative Procedures Act.

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DR. KADO: Currently, California has a one-hour standard for nitrogen dioxide of 0.25 parts per million. In comparison, the current national ambient air quality standard for nitrogen dioxide, initially adopted in 1971

and last reviewed by the EPA in 1995, is an annual standard of 0.053 parts per million.

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DR. KADO: The Important regulatory steps for the standard review process are summarized in this slide.

First, ARB and OEHHA staff and several contractors reviewed the scientific literature including chemistry, exposure, emissions, welfare effects and health effects of nitrogen dioxide. The results of the review are presented in the draft technical support document and are summarized in the draft staff report.

Further, the findings of this review formed the basis for the recommendations for the standards provided by OEHHA. These recommendations are described in the draft staff report.

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DR. KADO: The draft reports and the recommendation were released for public review and comment in April. They Air Quality Advisory peer reviews the report during the public meeting and comments on the report and its recommendations in writing.

All public comments in the first draft of the report go to AQAC for their consideration of the peer review process. And the public can also submit comment at the AQAC meeting for consideration.

The reports are revised as necessary in response to comments from AQAC and the public.

And, finally, the revised technical and staff reports are published, with a 45-day public comment period prior to the presentation to the Board at the Board hearing.

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DR. KADO: The California Health and Safety Code requires that the scientific basis of ambient air quality standard recommendations be peer reviewed. The Air Quality Advisory Committee fulfills this important function. The members are appointed by the President of the University of California, and each is an expert in one or more of the subjects discussed in the staff reports.

AQAC will review the report and recommendations in the current public meeting; also considers comments by the public, as mentioned; and then provides a written evaluation of the report and proposed standards.

As also mentioned, this evaluation and comments submitted by the public are addressed when ARB and OEHHA revise the draft staff report prior to the official 45-day public comment period prior to the Board hearing on the recommendations.

I would now like to transition from the standard review process into a brief summary of the staff's review

of the ambient air quality standard for nitrogen dioxide.

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DR. KADO: Staff of the Air Resources Board and the Office of Environmental Health Hazard Assessment, or OEHHA, along with several consultants, reviewed the scientific literature on nitrogen dioxide. The findings of that review, as mentioned, are contained in a draft technical support document which includes the information that we had mentioned, including human health effects, welfare effects, public exposure, air quality and atmospheric chemistry of nitrogen dioxide.

Based on the results of that review, OEHHA's made recommendations for revising the nitrogen dioxide standard.

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DR. KADO: I would like to acknowledge the many authors who contributed to the documents. And these included staff from ARB and OEHHA, as well as consultants who are experts in their field.

I'd like to begin by discussing sources, emissions, trends in nitrogen dioxide equality before turning over the presentation on the health effects and OEHHA's recommendation to Dr. Bart Ostro.

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DR. KADO: To begin, nitrogen dioxide is

typically formed from high temperature combustion such as present in gasoline or diesel-powered engines. It is also formed in air from complex atmospheric reactions starting from nitrogen oxide. Nitrogen dioxide is also present in indoor environments typically associated with the use of combustion appliances such as gas stoves.

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DR. KADO: As mentioned, nitrogen dioxide is both directly emitted and is also a byproduct of atmospheric photochemical reactions of other nitrogen oxide chemical species referred to as oxides of nitrogen, or NOx.

This figure illustrates the emission trends of oxides of nitrogen by source category expressed as tons per day. As indicated in this slide, mobile sources depicted in the light blue and yellow are responsible for the majority of the total statewide NOx emissions, for example, in year 2004, to be illustrative. The darker blue on the bottom of the figure represents emissions from stationary sources.

As seen here, the NOx emissions from mobile sources have been decreasing over the last two decades, and our expected to decrease in the future.

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DR. KADO: The South Coast Air Quality Basin includes California's largest metropolitan region. And

this figure illustrates the trend in the airborne concentrations of nitrogen dioxide.

The boxes connected by the solid line are statistically calculated values to determine the attainment as well as improvements in air quality, while the individual dots are maximum values reported.

The South Coast Air Basin has come a long way in reducing NO2 levels. For example, in 1988 the maximum one-hour concentration was 0.54 parts per million, more than double the state and one-hour standard. In 2004 it had declined steadily to 0.157 parts per million. And the State one-hour standard of 0.25 is illustrated by the dashed red line.

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DR. KADO: The annual average nitrogen dioxide concentrations for the last nine years for the highest individual monitoring site in the South Coast area is illustrated in this figure. The bars represent the annual average concentration for specific years.

As with the one-hour maximum level shown in the previous slide, the annual levels are decreasing. This trend is observed at other sites in the South Coast Air Basin, for example.

I would now like to turn the floor over to Dr. Bart Ostro of OEHHA for the presentation of health effects

of NO2 exposure and recommendation for a revised standard.

Dr. Ostro.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Thank you, Norm.

Welcome to the AQAC, members. Nice to see you here in beautiful South San Francisco.

First I do want to acknowledge the people who played a role in developing our recommendations a reviewing the science. And these people will be appearing when we get into the specific sections.

Besides myself, there's Janice Kim to my left, who is responsible for the study on the human clinical studies; Shelley Green, behind me, was involved with reviewing the epidemiologic literature; Daryn Dodge, Toxicologist, is back here as well and, along with Bob Blaisdell, helped develop the toxicology sections; Melanie Marty is the Chief of the Air Toxicology and Epidemiology Branch, so overall in charge. And George Alexeeff I think is here, our Deputy Director for Science for OEHHA.

Indeed, as we -- also was mentioned, we had several consultants help to pull together some of the initial literature review: Mark Frampton and Francesco Forastiere and Annette Peters, both from Europe where NO2 is taken a lot more seriously I think than it is here in the states. So Francesco's here today with us. We're

happy to have him. Francesco's been involved with a lot of epidemiologic studies in multi-city centers -- multi-city studies throughout Europe. And he's also been involved with helping us set guidelines and standards throughout Europe. He's been here with me for the last couple days. And we decided that in addition to having an NO2 standard, we should probably develop a pizza standard here in the Bay Area. There's some real quality issues that we need to address. So we'll get into that later tonight, I think.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So on to the actual recommendations.

We have recommended to retain the nitrogen dioxide as the indicator of nitrogen oxide pollutants. We have recommended lowering the current one-hour standard from 0.25, as Norm indicated, to 0.18 parts per million not to be exceeded. We've recommended establishing a new standard, an annual average standard of .030, three digits there not to be exceeded, and to retain the current monitoring method that we now have.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: And just to provide context where these numbers are, sometimes it's easier to -- when you see them

all at once. As Norm mentioned, there's a federal annual standard of .053. So we're proposing a lower standard on the annual side of .030. And we're also going to be tightening -- or proposing tightening our own one-hour standard. And there's no current federal one hour standard out there.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, as an in the case of ozone and particles, we draw on many different types of studies in our review and in our recommendations. So we used both controlled human exposure studies as well as animal tox and epidemiologic studies. And it turns out when you look at all the different types of studies together, you do get a fairly coherent picture of the effects of my nitrogen dioxide. So we draw on all these studies. And of course all the different types of studies have both strong advantages as well as limitations, and we take those into account as well.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So first on to the human exposure studies, the so-called chamber studies, where human volunteers are exposed in a laboratory setting to a well defined concentration usually of several minutes or

several hours of NO2. There are many different responses that have been studied in these efforts, including respiratory systems and changes in lung function, inflammatory markers in the lung or blood, and some cardiovascular effects. And typically in these studies, as in the case of ozone, they've typically involved either healthy individuals or generally mild adult asthmatics. There's some exceptions to this, but this is the predominance of the study subjects.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: Now, the advantages of these types of studies are that we have a very precise measurement of NO2, we know exactly what the amount is to which people are being exposed, we have very carefully discerned responses in the chamber. So those are characterized very well. So if we see something, we know it's indeed related to NO2. But the limitations are as follows: The biggest one is that there have been very -- generally very few studies particularly relative to ozone on -- and particularly on vulnerable populations. Of course we're typically studying relatively mild asthmatics, and asthmatics that are not currently experiencing respiratory infections, so it's a really selected group. And typically not looking at people with severe heart disease

or severe lung disease and so on.

The sample sizes tend to be relatively small. There are several studies with 8 or 12 or 15 subjects. And only very selected study doses. We don't have the full range of doses that we would like to see. There's very few studies of pollutant mixtures to which we know people would actually be experienced -- exposed to in the real world. And there's really no exposure -- no studies on longer term exposures from this literature.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Trying to summarize these findings, we generally have seen that among healthy subjects there's generally no effects at currently relevant exposures. Most of the effects we see above one ppm roughly in order of magnitude above what people are typically exposed to from ambient NO2. So most of the attention has been focused on asthmatics.

And among asthmatics we have observed two general effects in these human chamber studies: First, an enhanced airway response to allergens, generally a .26 ppm for a very short-term exposure, for a 15 to 30 minutes; and increased airway reactivity, at roughly .2 to .3 parts per million, again at relatively short-term exposures, 30 minutes to 2 hours.

The airway response studies are fairly robust. They've been repeated. And they show that when asthmatics are exposed first to NO2 and then roughly .26 ppm after a brief period, then exposed to pollen, they experience a greater allergic response than those who are exposed to clean air and pollen. So that's a significant response to -- enhanced response to allergy is observed.

And putting both of these sub-clinical effects together, we believe it suggests that NO2 is going to contribute to the ongoing pathophysiology of asthma through these types of mechanisms. So it's an adverse effect on that basis, that these things can be leading towards both increased exacerbation, increased symptoms as well as use of medication on the part as asthmatics.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, overall looking at all the different clinical studies together, we had several observations that I wanted to go through relatively quickly. And we certainly can discuss all these things more when we get into the appropriate section.

But, first, it's very clear that there's -- the evidence is very mixed regarding the effects of NO2 at low levels. I think we were all somewhat spoiled when we reviewed ozone and we had 20 studies or so all showing

effects at the same -- relatively similar concentration. Here at the same concentration sometimes we have positive studies and sometimes negative studies. So we certainly don't want to leave the impression that there's a consistent body of evidence showing effects at lower levels.

The evidence is mixed. And it appears to depend on the endpoint that's studied, whether it's lung function or symptoms or airway resistance or enhanced allergic response. Also it varies by protocol, whether it's at rest or exercising subjects the length of time they might be exposed to underlying conditions. It varies a lot by subjects, because asthmatics are very sensitive to a whole range of exogenous factors. So depending upon their own intrinsic susceptibilities and what they've been exposed to, we also see different responses from asthmatics, both do clean air as well as to NO. And also we see variation based on the phase of observation, whether it's early phases, within the first couple hours, or late phase examinations, say, after three or four hours up to 24 hours.

Now, that being said, we do see, as I've indicated, fairly consistent response for the enhanced -- in terms of enhanced allergen.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: And this next table just indicates the studies that have found effects at .26. The top study found effects at .4, the Tunicliffe study, and didn't find anything at .1. But the other studies all found effects at .26, 30 minutes or 15 minute exposures. And you see the different types of markers that have been found indicating allergic response, everything from FEV changes to peak flow changes to markers of inflammation, the PMNs and the ECPs. So we we've seen a wide range of effects in terms of the allergic response.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Regarding the airway reactivity, however, the findings are much more mixed. As I've indicated, there's several negative studies, between .1 and .3, the relevant range of exposures for people in California in general.

That said, there are several positive studies that are of concern to us. And just reviewing them very quickly -- again, we can discuss these more in detail. But the Orehek study in 1976, basically showing fairly mild effects on airway reactivity, but showing effects down to .1 -- a one-hour exposure of .1. And he indicated that 13 of 20 asthmatics had a positive airway reactivity

at those levels.

The Ahmed study, which is really presented only as an abstract, also showed effects at .1, with also about three-fourths of the subjects responding.

The Bylin study, again .26 in 30 minutes, showing effects at .26 statistically significant group level effects, and almost a hint of an effect at lower levels, at .13, with a statistical significance of .052. Given this was only eight asthmatics -- eight mild asthmatics, the .052 is not something to totally ignore in terms of the importance or the statistical significance of the group effects. So there's a little hint of an effect at lower levels.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Here we have the very famous study from Kleinman in 1983, showing effects at .2, two-hour exposures. I think it would be fair to say that Dr. Kleinman had a lot of caveats on this study. The effects were very mild and there was a lot of effects on lung function and so on where there was -- nothing was seen statistically. But, again, did report that two-thirds of the subjects had a positive airway resistance after the .2 parts per million.

Strand at .26, 30 minutes. Again, a slight

increase. A P value of .08. But statistical significance after -- at the late phase of five hours in terms of a group effect for airway resistance.

Another effect from Jorres & Magnussen, a .25, 30 minutes.

A Bauer study at .3, 30 minutes.

And then Follinsbee did what I would call a fairly soft meta-analysis of all the studies up to that point, up to 1992, and indicated that about -- again, about three-fourths of the subjects had a positive airway resistance response at rest between .2 and .3. And also indicated there was some hint of an effect at .1.

I'm sorry. I keep saying airway resistance, and I'm meaning airway reactivity. So sorry about that. Airway reactivity we're talking about.

So taken together OEHHA believes that there's concern for effects down as low as .2, there's some evidence for some response by some individuals; and, again, with even some evidence that Follinsbee indicates that there's some suggestion of effects even lower, in the .1 to .2 range, in these studies.

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EHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, other general observations that we have observed, that we put together when we look at all

literature together, is extreme variability in the response among subjects, as I've already indicated. The asthmatic subjects that have been looked at, sometimes the studies are replicated with the same concentration and you don't see any response among the asthmatics; some asthmatics respond very strongly within the given study. So that's been an observation in a lot of these NO2 studies.

There's a little bit of evidence for non-attenuation. Remember, in ozone we tend to see an attenuation after the first day or so of exposure. There's only a little bit of evidence for this. But in the Strand study we did see that after four days of exposure to NO2 plus allergen, the subjects were still responding.

We also see some evidence of some larger responders. And I've indicated some of the magnitudes, 3 of 15 -- 3 of 20 in some of these studies. And sometimes in studies even when there was a negative group mean effect or a null group mean effect where no statistically signifcant difference could be observed, there were still some responders -- some individual responders among the asthmatics, even mild asthmatics.

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SUPERVISOR OSTRO: There was also a few studies on people with chronic lung disease. Two studies I think decreased lung function at .3 parts per million, something to the throw into the mix. And then a general observation that there's very limited data for children, elderly, those with cardiovascular disease, and those were longer -- and studies with longer exposure duration. I mean the biggest concern here among the subject population is that the asthmatics that have been studied are generally very mild asthmatics, again not with any kind of respiratory infection or any other problems at the time. But some of them were even allowed to take some of their medications; usually not broncho constrictors but -- broncho dialators, but some other medications were maintained during the study period.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: So on to the toxicology studies. Again, we believe that these toxicology studies generally are supporting the findings of both the epi and the clinical studies. The oxidant damage mechanism is consistent for both the animals and the human studies. There's evidence of inflammatory responses at .5 to .8 at very -- relatively short-term exposures.

In animal models of allergic asthma, as we

indicate in the slide, exposures to very high concentrations, at 5 ppm, produce increased markers of allergic inflammation. We see these same types of findings in epidemiologic studies at very low levels. And also the tox study showed that prolonged repeated exposures of young animals during lung development showed changes in lung structure, again at .25 ppm. So, again, we see airway reactivity and enhancement of allergic responses in these toxicologic studies.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: On to the epi studies. Again, these studies evaluate exposures and responses in free living populations over a wide range of different types of individuals, different behavior patterns. We can look at different subgroups and particularly look at susceptible individuals, including not just mild asthmatics but a whole range of asthmatic and non-asthmatic individuals.

These studies examine both the short-term effects -- in this case we're talking as short as one hour, but usually a 24-hour exposure -- as well as long-term exposures, studies of up to several hours.

The limitations of these studies are -- unlike the clinical studies, the chamber studies, it's difficult to determine the specific exposure averaging time even if

they're measuring -- or if they're measuring of one-hour exposure in the study, we can't say clearly that it's only a one-hour exposure and not an 8-hour or a 24-hour or even a multi-day exposure that might be relating to some of these things. So it's harder to determine the specific exposure period. And it's exposure average time that's important.

And most important with these NO2 studies is the important need to account for other factors, particularly co-pollutants that are also part of the products of fuel combustion that are related to NO2. So, for example, in terms of spatial changes we would see NO2 varying with distance, say, from a roadway. We'd also see ultrafines and elemental carbon and maybe even VOCs spatially having a similar pattern as NO2. And then when we talk about time series studies where we're looking at concentrations day after day after day, typically we see very high correlations between NO2 and particles, particularly PM2.5, but with other things as well.

So one of the issues that we deal with with NO2 is whether it's truly an NO2 effect or whether it's an effect of a whole mix of other pollutants, and that NO2 might be just a marker.

Now, we do see from the tox in human studies that NO2 itself does have effects on asthmatics in terms of the

allergic sensitization. So we have some reason to believe that at least some of these effects are NO2 specific. But it's an ongoing concern in these epi studies about the role of NO2 versus that of some of these other pollutants. So studies are trying very carefully to control for other factors, other pollutants.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, in terms of the epi studies, there's lots of different types of studies that we're able to draw on. And I'll just briefly mention the different types and some of the evidence from them.

First, there's outdoor time-series studies. Again, very similar to the ozone and particle types of studies.

There's outdoor panel studies, where a subset of people like asthmatics are studied over a two-week to three-month period every day, where we're really looking at individual data. This is in contrast to the outdoor time-series studies where you're really looking at group effects. You're just looking at total counts of mortality or morbidity on a daily basis.

We also have traffic studies since NO2 correlates very well with traffic in most of these studies. So some studies simply use a proximity to traffic as a marker of

exposure, and with the inference that these are NO2 and related effects of pollutants.

There's also outdoor chronic studies that I'll be talking about briefly, and then the indoor gas-stove-related studies that were fairly popular in the nineties.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So what do these studies tell us? In terms of outdoor studies, short-term exposures -- and, again, we're talking about usually 24 hours, but sometimes several days -- there's been associations reported with daily mortality, and then cardio and respiratory specific hospital admissions and emergency rooms, including ER visits and hospital admissions for asthma. There's all sorts of cardiovascular effects including arrhythmias and some other types of endpoints. We see effects on asthma symptoms and changes in lung function from these types of studies.

There's also an important point, that among all the different endpoints it does seem that the respiratory effects, especially those for asthma, appear to be most consistent for both adults and children. And I'll talk about these two different types of studies now.

First, regarding the long-term -- sorry -- the

short-term time series studies, these daily mortality studies, we do indicate in review that there's evidence from these time series studies of mortality effects.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: Now, in the U.S., for example, the end-map study by Samet, et al., which we've talked about regarding both PM and ozone, also included NO2 in the model. It's a study of the 90 largest cities in the U.S. And in single pollutant models when NO2 is the only pollutant after controlling for time, weather and other factors, they do find an effective NO2 on daily mortality. However, when they add other pollutants into the model, particularly PM10 in this case, the NO2 effect is attenuated. The magnitude of the effect was about the same, but the standard error -- as the confidence intervals included one, the standard errors increased, and they were no longer statistically significant. And we can discuss in the -- during the epi section the relevance of a two-pollutant -- multi-pollutant models. Different people have different opinions on that, on how useful those are. But it was the case that in the U.S. study -- in the biggest U.S. study, the NO2 effect was significantly attenuated when other pollutants were added into the model.

Now, in contrast to this, in several European studies, the NO2 effect held up in multi-pollutant models. There's recently a paper by Samoli, followed up by these APHEA studies, the air pollution studies in Europe, a study of 29 European cities. And they find an effective NO2, and the effect of NO2 holds up when other pollutants are added into the model. And you see a concentration of -- the median concentration among the cities of around 28. So figure a mean of 30, 32, 34, around that range in these European studies.

The Biggeri study in Italy was not a multi-pollutant model. It was only NO2 model, but did find a statistically significant effect with a mean of 39 ppb in eight cities.

And then the two other studies, the Burnett study in Canada and the Saez study in Spain, again found effects of NO2 as a single pollutant as well as in multi-pollutant models, so that NO2 effect seemed to be maintained.

And one other thing to note is that there also seems to be an NO2 interactive effect or an effect modification that Katsouyanni 2001 study, again an APHEA study of 29 I think European cities, showed that there was a particle effect in those cities; and in those cities that had higher concentrations of NO2, the particle effect was larger, indicating that maybe where NO2 is a proxy

maybe for traffic where areas had higher traffic-related particles, the particle effect tended to be higher. So we did see this effect modification in that city.

Not many U.S. studies that have looked explicitly at NO2. Most of the U.S. studies, you know, we've all become so particle centric, so most of the studies look at particles. And then they look at NO2 just to see if the particle effect goes away. So there hasn't been at all the level of sensitivity analysis and care taken to see what happens with NO2 in different types of models. So not a lot of evidence from the U.S., which is one of the shortcomings that we're dealing with here. Most of the studies we're drawing from here and with the asthma outcomes are from Europe.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, as I indicated, the asthma findings tend to be a lot more robust. And here are seven studies. And I added another one at home on Saturday, but I neglected to add it to the -- I added it to my own presentation at home, but I didn't add it to this presentation. So I'll just mention those two other studies.

But all of these studies NO2 had an effect on either asthma emergency room visits or hospitalizations.

And in all of these studies -- I selected these studies because PM was either not related to asthma in these cases or was included in a model with NO2 and the NO2 effect was maintained even when particles were considered in these models.

So here's seven models and with the year and the principal author, the type of the health effect that was considered, and then at the end in parentheses the mean of the study exposure in terms of parts per billion. So you can see effects from roughly, I'd say -- if you look at the last study, that these are median -- so the mean might be around 30, from around 23 in the top study, the Peel study, to around 57 in the London study.

Now, the Peel study is unique in that it's the only U.S. study that I could find that showed a clear NO2 effect in multi-pollutant models on asthma emergency room visits in children in Atlanta.

And, again, even if you do find an NO2 effect, it doesn't mean it's NO2. Again, there are other things that will move with NO2 over time. Nevertheless after controlling for particles, there was still an NO2 effect in Atlanta. The other studies, all European, again see a persistent NO2 effect.

The two studies that I didn't include on this slide, one was a study by Linn, et al., which found effect

on hospital admissions for asthma in Toronto. And in another U.S. study, there's a study by Norris, et al., 1999, which did not find an effect of NO2, and was at a concentration of around 20 in clean Seattle. So the concentration of 20, no effect seen in the U.S. study in Seattle.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: So the second -- other types of studies that I've talked about regarding epidemiology are these asthma panel studies, where several asthmatics anywhere from 10 or 15 up to 150 are followed on a daily basis and their symptoms and lung function are recorded, along with ozone or NO2 or particle concentrations. And you can see again several studies from the panels indicating effects of NO2. We have a series of Delfino studies, again the king of the panel studies here as an ozone, finding both symptoms and wheeze in southern California children.

Again, in these studies a lot of co-pollutant concerns. When multi-pollutant models were examined, sometimes NO2 loss statistical significance. So it's hard again to say from these studies that it's clearly an NO2 effect. But there was at least a positive association with NO2 in this model, as well as with the Mortimer model which looked at peak flow in eight U.S. inter-cities.

A study I did in south central L.A., African American children, we found symptoms relating to NO2.

A Dutch study found symptoms among children who already were hyper-responsive.

And a Linaker study showing that after a week of respiratory infection that higher levels of NO2 were related to symptoms relative to lower levels of NO2. So an important effect of respiratory infections and NO2 shown in that study.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, moving on to the longer term studies, these studies include both exposure -- or measurement of NO2 and sometimes no measurement of NO2 but just measurement of traffic. And just to broadly characterize these studies, measuring traffic have found -- and, again, exposures are measured anywhere from one year to four years or more -- have shown relationships with exacerbation of asthma, reduced lung function and lung growth; there's some studies showing low birth weight in newborns and respiratory symptoms, all relating to traffic or NO2 broadly measured.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: I wanted to point out our study funded

by the Air Resources Board.

The Gauderman studies, a series of studies in southern California -- and this study published in 2004 -- 12 communities in southern California were examined. The cohort was examined for lung function growth in children ages 10 to 18. And they found a higher percentage of children with FEV1 less than 80 percent at the older ages, indicating a more -- a likely permanent loss in lung function certainly among the girl, whose lung development would be slowing down at that point or ending at that point.

And they found that in areas that had higher NO2 as well as higher PM acid vapor and other pollutants, some measured and some not, there was effects. And I just draw your attention to that -- in this graph, we tend to look at all these cities together, in a way, as high NO2 cities or versus low NO2 cities because there's always going to be some measurement error in each of the cities, depending upon where the monitors are placed. But, in general, we say that in the range of roughly 28 to 40, with a mean of around 33, 34, we see an effect from all these co-varied pollutants, again NO2 plus other things. But in this -- you would see a same graph if you looked at other pollutants. But here is the NO2 effects again showing effects roughly in the 30, 35 part per billion range, a

very important endpoint here.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Among the other long-term studies there was another part of the cohort, 2005, that showed higher NO2 concentrations relating to a history of asthma. So we're talking about potential asthma onset as well as current asthmatic conditions, both wheeze and medication use, relating to again both NO2 and traffic in this study.

Dr. Kim was the lead author of a study in the East Bay on exacerbation of asthma among children. And we found in that study exacerbation of asthma in bronchitis, at roughly 23 ppb. Again, hard to separate out NO2 versus a general traffic effect.

Two very interesting European studies:

Kramer (2000) showed allergic sensitization and allergic symptoms in German children at around 23 parts per billion. This is longer term exposure.

And, finally, a Janssen study finding allergic sensitization, measured by skin prick tests as well as IGE, in Dutch children at a lower level. She had stronger findings relating to truck traffic. Just being close to a lot of trucks showed an even stronger effect. But they did measure NO2 in this study and found effects relating to that in terms of allergic sensitization.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So we do see this common pattern among the epi clinical and tox studies over this allergic sensitization leading towards symptoms of astha and then also medication use.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, in this figure here I tried to just summarize for AQAC the studies that I've just indicated.

Studies 1 through 6 are these time series studies. And I think you have on your handout, if you want to identify the specific study. So 1 through 6 are the asthma emergency room visits hospital admission studies.

And studies 7 through 11 are the long-term studies relating to allergic sensitization and lung function changes.

And then we've put the averages in the diamonds here among the different studies.

And, again, two studies are missing that I just talked about. One would be showing in effect a 25 in Toronto and a null effect at 20 -- or non-statistically significant effect at 20 in Seattle.

And, again, I want to be careful about indicating that there's a lot of negative studies that are not on this chart. So I could easily present 20 studies that don't find effects of NO2 on asthmatics' emergency room visits and hospitalization. It is a relatively low frequency event. And these epi tools looking at daily changes are not a fine tool. So to find any kind of effect I think is somewhat surprising. So there is a lot of negative studies and they're in tables and we've discussed them in the text. So I don't want to leave the impression that all the studies are consistently finding associations.

But it is important to know that there are several carefully done studies that do find effects from NO2 after particles have been taken into account in these models, at least in the time series model.

Again, in the longer term studies you have the co-variation of NO2 and a whole set of other pollutants, so particles really cannot be taken out in those studies. But you can see broadly that we see effects roughly in the 20 to 50 range, with a real set of numbers in the 30s that we tended to focus on -- in the 30 to 35 range. And, again, for comparison, the current federal standard for the annual average is 53 parts per billion.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So this I think you have in your handout just summarizes the different studies that are in the table, so I don't have to go over that.

Now, we also have a set of indoor studies which I've indicated were much more popular in the nineties. I don't think there are as many indoor studies that people are undertaking these days. But we knew that gas stoves were a source of NO2 and other species as well, probably ultrafines and particles and several other things. These studies looked at long-term exposures, of weeks to months. And taken as a whole, they indicated respiratory symptoms among asthmatic children and infants at risk of asthma. So, again, indicating a potential NO2 effect or effect in homes with gas stoves so it could be other constituents relating to that.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So taking all these studies together, what is our basis for our two standards? And I want to briefly indicate that now.

First, the one-hour standard, as we've indicated, we're recommending dropping from .25 to .18 parts per million. And our basis is as follows:

First, since our last review in 1992, there have

been several more important studies, particularly the allergic enhancement studies, at levels of .25 and below, indicating effects.

Second, we have the airway reactivity studies that I've reviewed indicating a mild response but some response among asthmatics -- mild asthmatics in the .2 to .3 range 30 minutes to 2 hours.

And, again, I've indicated that there's some hint of effects even below this level, so .2 or .26 are -- .26 in terms of the allergy studies are not clear threshold, no effect type levels.

So we see the airway reactivity studies finding effects in the .2 to .3 range, maybe lower, short-term exposures; the allergic response at .26; and modest associations in the few studies that have been carried out below .2.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: We also thought it would be important to add a margin of safety for the fact that these studies include generally mild asthmatics. So we add a margin of safety for children and other susceptible population, particularly more severe asthmatics, asthmatics with respiratory infections, asthmatics who are not using their medication or don't have proper medical accessibility, and

other possible endpoints. I haven't said very much at all about cardiovascular endpoints. But there's some studies at higher levels indicating potential cardiovascular endpoints in these clinical studies.

So there's that. There's the possibility of effects at lower levels that haven't been really tested carefully. I mentioned a few of the studies at .1 and .14 that are mildly suggestive of something going on.

We also wanted to make sure that the margin of safety included the averaging time. Since we're proposing a one-hour average and some of these studies have found effects after 15 to 30 minutes, we needed to lower the levels from .2 or .26 to take into account that we have a longer averaging time.

And the fact that we have epi studies that we've talked about. And the Epi studies also may be due to one-hour exposures. In fact, some of the studies have used one-hour exposures. We can't say it is the one-hour exposures per se that are driving these effects. But some studies do find effects from the one-hour exposures at lower levels, and we can't preclude the possibility that something's going on at these lower levels.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So for these reasons we've proposed a

standard of .18 parts per million for the one-hour average. Now, you may ask why did we stop at -- well, you won't ask this. So we'll talk about that for the one-hour standard. So for this we've gone to .18 for our recommendations.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, regarding the annual average we've proposed a .030, which is a new averaging time for California. And our reasoning is as follows:

There's potential effects on very serious outcomes including mortality, ER and hospitalation for things like arrhythmias and lung development.

I've indicated that in the range of .25 to .5, broadly speaking, that we see more robust results for hospital admissions and emergency room visits for asthma as well as long-term effects on various endpoints from NO2 exposures in these ranges.

We also have the recognition that NO2 is likely to be a good marker of traffic. We've seen all these effects from traffic. Again, we don't know for sure it's NO2, but there's some potential role that NO2 is playing in here and we incorporate that in our thinking.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: We also add that tox studies are showing the airway reactivity and the enhancement of allergic response, and also a potential alteration in lung structure. So we think about that in terms of margins of safety.

And we also think again that we might -- a one-hour standard by itself might not be fully protective, that some of these effects might be from multi-hour or 24-hour or multi-day exposures. So we think it's important to lower the full distribution of NO2, not just the one hour. So this is where I was going to say that you might wonder why we stopped at 30 parts per billion. Maybe there's evidence from the European studies to go lower, and I just wanted to say a word about that.

First of all, in the -- I've indicated that the NO2 is of course correlated over -- it's spatially with ultrafines and elemental carbon and other constituents as well. And it's correlated over time with -- when you're doing these daily studies, these daily time series studies, it's correlated with PM2.5, usually correlation coefficients though between of .4 and .6. So even with multi-pollutant models it's -- you can't say clearly it's an NO2 effect. If we knew clearly that these rather severe effects were occurring at -- were due to NO2, we would drop the levels even lower. And we can discuss

AQAC's view on all this evidence taken together and on our thought process here.

But since most of the studies were European studies, there's a lot of negative studies -- we haven't seen much positive studies in the U.S., we thought the studies were important enough to have an annual average that would add protection to the one-hour average. But at this point we said based -- we thought based on the lack of U.S. studies, that we wouldn't go much lower than the 30 parts per billion.

And then there's the issue of in fact extrapolating from the European studies. Now, if all of these effects are one-hour exposures, let's say even the epi studies, then outdoor NO2 is outdoor NO2 and we don't have to worry about extrapolating. So if you see effects at .2 or .25 or .3 in Europe, you would see the same effects here.

But if the effects are longer than one hour, then you have to think about longer term exposures. You have to think about 24-hour exposures. You have to think about exposures indoors. And the evidence in the U.S. where we have the tighter homes and a little bit further distance from traffic to home relative to Europe, the evidence seems to suggest that, you know, the penetration rates with NO2 are not that high. Sometimes there's very little

correlation between personal NO2 and outdoor NO2. So we just thought that we couldn't easily extrapolate from all of these European studies to U.S. concentrations when you factor in the indoor penetration.

And the fact that NO2 in Europe is also relating to diesel, which are much more common in Europe than they are here, so there's also an ultrafine, a diesel elemental carbon effect that might be concurrent with NO2.

So we put all these factors in and we thought at this point in time, pending additional studies that we expect to see over the next couple years on NO2, that we would start with a 30-part-per-billion annual average.

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OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So, again, just our numbers here of our recommendations, where we are.

And I think that concludes my presentation of our recommendations.

Thank you.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: We're actually scheduled right now to take a break. Would you like to do that, Dr. Kleinman, maybe about a two-minute break?

CHAIRPERSON KLEINMAN: Yeah, I think that'll be a good idea.

What I'd like to do after the break is at that point we're going to open this up to the Committee members to review this. And just looking at the program for the rest of the day, what I'd like to do is -- in the afternoon after the break we'll be talking about the staff report and, you know, our comments on that and our comments on recommendations at that point.

So what we'll do is after this break we will start looking at the technical support document issues and go through the various chapters on that. And then we'll take the staff report, which is an integration of that technical support document, and we'll look at how well the integration worked and were there gaps in the way things were brought across.

So with that, why don't we take a ten-minute break.

And is there a -- I guess we have to go over to the hotel to grab coffee, is that --

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: I think so, yeah.

CHAIRPERSON KLEINMAN: Okay.

(Thereupon a recess was taken.)

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Okay. So, Dr. Kleinman, this is the time I guess for your committee to do their peer review. But I'd like

to make a couple of remarks at the beginning just to kind of remind you that, you know, your group of course does the peer review of both the technical support document, the integrated staff report and the OEHHA recommendations and -- the Air Resources Board.

Of course what happens after this stage is ultimately the staff will put together in the final staff report, which will be based on this Committee's findings and recommendations -- in fact, probably modify the draft document based on that. So you're comments are very important to both the Air Resources Board and OEHHA in that ultimate process itself.

And kind of reminded me, we did -- ARB and OEHHA staff did get together and we sent you some questions I think about two or three weeks ago, which was along with some of the guidance you'd given your committee, that we wanted the Committee to be aware of too. And a lot of those dealt things -- are the effects -- the health effects from the controlled studies sufficiently adverse enough. And it gets back to the definition of what's an adverse effect.

We also brought up some of the -- on the longer term studies and these multi-pollutant studies, how to interpret those kind of standards. I think we gave you a list of about seven questions there. So hopefully your

committee can weigh in on those heavily as well.

So with that, I'll let you take over.

CHAIRPERSON KLEINMAN: Sure.

What the Committee's done is, depending on the expertise of the individuals, we've all read one or more of the chapters in the technical support document as well as the staff report and the list of questions that were sent to us through ARB. And what I'd like to do is start out with the first four chapters dealing with the chemistry, the exposure, and the monitoring. And we'll have Dr. Green start off and then other members of the Committee who have comments on those chapters can weigh in.

So let's start with that.

ADVISORY COMMITTEE MEMBER GREEN: Thank you.

The first chapter in terms of introduction overview I think is very straightforward. It covers the appropriate relevant issues. And I didn't find any gaps or errors or references missing I would have liked to include. It's fairly brief of course.

The next chapter concerning physics and chemistry of NO2 is really my field and something where I'm working on related issues recently and currently. And I think it's also a quite complete chapter. The interaction of NO2 and other species in the atmosphere, like ozone and

photochemical reactions, sources, sinks, long-range transport via compounds like peroxyacetyl nitrate and other peroxynitrates are all important, all somewhat complicated, but issues that have been studied for many years now and are generally understood quite well. There will be ongoing research. There will be new details learned and things will change on regional and global scales.

But I think it's covered quite well here, and there are certainly no large unknowns in the picture of NO2 and the physics and chemistry of the atmosphere that produce it and destroy it as it comes and goes.

It's aside from this group's mandate or this regulation's applicability. But I think the interplay with ozone is very, very important in that California and other regions have challenges ahead in meeting desired ozone targets. And that will probably only be achievable with concurrent improvement in NO2 concentrations.

So I think -- although it's outside the issue immediately at hand, I think this will be an action that will have additional benefits in here air quality for the public health of Californians and more broadly. So outside our immediate concern, but I think important and beneficial.

The third chapter concerning measurement, that

is, the assessment of actual exposures, is also an area where there are complicated chemistry issues exposure to other pollutants at the same time, time scales of measurement and so on. But, again, it's a field that has been long established, technologies have been developed and confirmed. And I make NO2 measurements in my lab.

It's certainly very complicated assessing exposures of indoor versus outdoor, but that's spelled out here and acknowledged. And it's again complicated, but that complexity is understood. There will be future progress in monitoring and in distinguishing the fine details involved. But there are no major mysteries. It's a well established field. It's been quite a long time since there's been a review or update or change of measurement protocols, and I think it's fairly straightforward and well presented here.

I didn't find any missing references. I checked up-to-date literature quite recently to see if there were any, say, critical reviews reassessing any sort of picture. And there were not. There are ongoing studies involving NO2 -- NO2 and other pollutants, both in California, the U.S. and other countries. But there's nothing dramatically that has cropped up, so nothing that needs to be added by any means. Certainly any time several years pass you get many new studies. And there

will be minor changes in the years ahead, but nothing dramatic I would expect.

In terms of sources and emissions and the monitoring and the relevance of the exposures, I think it starts to border into the biological and clinical side. But it appears that the sensitive groups are well identified. Again, there are always fine details to be learned better as the years go by. But it seems straightforward that we know what sort of exposures to be looking at and looking for and considering. And one expects the details to evolve over time. But, again, things are well established. I didn't find anything missing that I would have wanted covered or referenced.

The monitoring apparatus is quite quantitative and is quite selective, that is, it doesn't give false measurements if something else is present in a mixture. So, again, it's fairly clear, it's appropriate to be regulating at precisely defined numerical standards.

The expression of the standard as a volume fraction is the right way to do it because that measurement is independent of atmospheric pressure changes due to weather or elevation. And we have a wide range of elevations in California, so I think that's the preferred type of unit to be using and referring to and establishing as a standard and measuring with the apparatus. Other

studies sometimes do the mass concentration. But that's actually something that has to be corrected for standard atmosphere, sea level and pressure. So it's preferable to keep it in the volume units.

It might be more convenient to more uniformally use preferably billion units, with a B, rather man million to save the extra decimal point and trailing zeros necessary for a specific two-digit number like 30. And, in fact, some chapters off and on through the material use those units because that's what things have been reported in. It doesn't really matter as long as the trailing zero is specified when appropriate.

Other regulations such as earlier ones in ozone have significant round-off flexibility that actually allows for marginally higher concentration to be acceptable. And one needs to be clear about that. And I think in this case things have been well spelled out. It's just a matter of convenience and clarity.

In checking my notes, I think those are most of my comments. Again, the first four chapters are fairly straightforward. They cover well established issues, issues that were in fact generally well established in the previous review cycle. And in the meantime incremental progress has occurred and minor changes, but nothing dramatic. And I would not expect dramatic mysteries to

suddenly appear. It's a perfectly well established regulation and it's a good time to review it.

Certainly on the clinical biological side, things are much more complicated, though well established and evolving. And I'll let others comment in all of their specialties.

CHAIRPERSON KLEINMAN: Thank you.

I had a few questions that I'd like to throw out. And starting in Chapter 1, which basically summarizes the history of regulations, one of the options that's available is the secondary standard to protect welfare. And the welfare standard was briefly mentioned in the staff document -- staff report. And we will talk about that in more detail. But it might be useful in the staff document, in a technical document -- support document to add that -- you know, some information on that into Chapter 1 because, if for no other reason, changes to the standard that will reduce NOx are certainly going to have an impact on the amount of fine particles generated. And as an extra benefit there'll be improvements in -- well, possible improvements in visibility. And so although those aren't, you know, key factors, I think it's important to add as much support documentation as we can.

In that regard, in Chapter 2, which discusses the atmospheric chemistry, given that, in southern California

at least, nitrates represent something like 50 percent at times of the winter time fine particles, it would be worthwhile mentioning or projecting what the impact of reducing the NO2 would be on the potential fine particle burden as well.

Now, I did have a question. And I'm not sure that, you know, we can deal with it completely now. But I wanted to ask about the peak indicator value that's used. From reading the chapter, it's made clear that this is the limit that you use to identify unusual spikes; and to eliminate, you know, values that are extraneous -- not extraneous but extra high and not necessarily representative of true exposures, and those could come about through, say, an accidental release or, you know, a malfunction -- a temporary malfunction in a source, a fire, something like that. But I was wondering, because it's not spelled out and I think it should be in the report, whether that peak indicator value -- because you provide graphs that show peak indicator values for each individual site, and then there's one for the state as a whole. And I -- my question is: Is that -- which indicator value is used to eliminate extra high values for a particular location? Is it the location's indicator value or is it the state's indicator value?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF

BODE: This is Larry Larsen from our Technical Support Division. And his group is in charge of area designation.

MR. LARSEN: The group of which I am a part of.

The values of the peak indicator are calculated on a site-by-site basis. They are applied primarily for determining attainment and nonattainment of standard that's in place. And they are done -- the attainment designations are typically done on a regional basis rather than a site-by-site basis. So the highest site in a region would be the determining factor for the regional designation as attainment or nonattainment. But values would be excluded from consideration essentially on a site-by-site basis. Although the highest site would be the governing site.

Does that answer the question as fully as you'd like?

ADVISORY COMMITTEE MEMBER PLOPPER: Could I follow that up.

Can you translate that into Table 5-2, where it says maximum one-hour value. So you're excluding all the peak values? I mean --

MR. LARSEN: Table 5-2?

ADVISORY COMMITTEE MEMBER PLOPPER: -- 5-2, page 513.

MR. LARSEN: In the staff report or technical

support document?

ADVISORY COMMITTEE MEMBER PLOPPER: Oh, I'm sorry. We talking about -- I'm talking about the main document.

CHAIRPERSON KLEINMAN: Yeah, this is the technical support document.

ADVISORY COMMITTEE MEMBER PLOPPER: This is not what we're dealing with now?

CHAIRPERSON KLEINMAN: Yeah. Page 513.

MR. LARSEN: No, maximum one hour that you see in this table is the measured maximum, not the highest that was not excluded. Is that the question?

ADVISORY COMMITTEE MEMBER PLOPPER: Still don't understand what you're talking about.

So in other words this is not actually the maximum value; this is the --

MR. LARSEN: No, it is actually the maximum value measured.

ADVISORY COMMITTEE MEMBER PLOPPER: It's unadulterated?

MR. LARSEN: Unadulterated -- unlimited.

ADVISORY COMMITTEE MEMBER PLOPPER: Unlimited. Okay. That helps, yeah.

CHAIRPERSON KLEINMAN: But for attainment you then exclude values if they're above the --

MR. LARSEN: -- if they're above that indicator, yes.

CHAIRPERSON KLEINMAN: -- the peak indicator value.

MR. LARSEN: That's correct. And they -- the performance of that process is that approximately one per year on average would be excluded from determining attainment or nonattainment.

ADVISORY COMMITTEE MEMBER PLOPPER: So -- this is Dr. Plopper again.

So which values do they use in these epidemiologic studies? Are they -- are the values that they use for determining local concentrations for epidemiologic studies, are those values based on excluding these max --

LARSON: No. The epidemiological studies would be taken all of the data available into account.

ADVISORY COMMITTEE MEMBER PLOPPER: Oh, okay.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: So what we really have here is like two sets of values, you're right. And one is for the standard as far as what the standard is and how many days you exceed the standards, the maximum values. And so all the health studies are using real data.

But this peak indicator I think came about back

because of a law in the Legislature -- what, about ten years ago? -- which was put in place for area designation, that is, which areas, you know, were in attainment for standard. And it put through a separate process, separate from the standard setting process that allowed -- as Larry has mentioned, allows approximately one exceedance a year from these short-term standards. So ozones is affected by this NO2.

MR. LARSEN: Uh-huh. Yeah, this is only applied to standards that are set for short-term, 24 hours or a shorter averaging time.

CHAIRPERSON KLEINMAN: Okay. Now, the downside to this approach is in areas like the north central coast where you've actually got increasing NO2 levels. You know, if you used the historical, you know, indicator value, you might exclude some real values that are, you know, brought from essentially new sources and new growth, and it's going to take a while for that -- over what period, I guess, do you, you know, figure out that peak indicator?

MR. LARSEN: The regulations currently have that done on a three-year basis. So it's a moving three-year window. The most recent three years are used to determine the current annual designation.

CHAIRPERSON KLEINMAN: Okay. So over time that

will continue to follow the overall trend?

MR. LARSEN: That's right. If air quality is worsening and NO2 levels were increasing, it would catch up with the area, the indicator response to that increase. If it's decreasing, you see in the charts that are provided some of the trends are dramatically downward because air quality's been improved.

CHAIRPERSON KLEINMAN: Great. Thank you.

ADVISORY COMMITTEE MEMBER GREEN: I realized I had one more comment on Chapter 4, if that's okay. It's not a shortcoming so much as a suggestion for additional studies and things to look for in the future.

Among the various sources you have for NOx in general are -- is the formation of NO2 from NO. And noncombustion sources of NO may be something that's under-recognized and under-inventoried in the non-urban parts of the state, particularly the San Joaquin Valley where summertime air is proving to be quite a challenge.

So looking at sources of NO from soil, grasses and trees, would be the kind of thing to look for. As the combustion sources are steadily cleaned up NO2 may level off because noncombustion sources are present and in fact may be increasing.

There will be a natural background of NO from natural soils, grasses and trees. But there's also a lot

of anthropogenic management of soils, grasses and trees through crops, fertilizing, manure spreading, composting, all sorts of noncombustion activities. And these are areas in which for reasons of business change, over the years new practices come into play, sometimes new practices come into play to address one regulation such as VOC reduction, which ought to help reduce ozone in the San Joaquin Valley. However, if the practice ends up causing a larger release of NO, which oxidizes to NO2 and adds to NOx, one could actually be working on one part of a problem but making another part of it worse, or at least not gaining ground overall, which we don't want in cases like San Joaquin Valley ozone in the summer where we really do need some improvement.

So I would suggest adding the noncombustion sources of NO2. It's indirect via NO, but it's definitely linked into the picture for the future.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Great. Thank you.

CHAIRPERSON KLEINMAN: One other comment on Chapter 4. There's the section dealing with the projections over the next couple of decades. And they clearly show the mobile source contribution dropping quite drastically, which, you know, is to be expected from new controls and new emission devices that are going to reduce

that. But it also shows very slight increases in stationary sources, which again is logical given increases in population and things like that.

But I was wondering whether in those projections a count has been taken of the recent shifts in the availability of fuel oil, the possible change of fuel sources over the next couple of years and whether we need to have more research done to better define that, or whether that's already ongoing.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Well, I will tell you, a lot of the decreases in trends right now has been from the switch from fuel oils to natural gases and also to the large trend in motor vehicle controls, especially heavy-duty diesel controls. So whether that long-term forecast -- you know, at this point I don't know. I don't think they really have those looked at and whether the -- you know, I know natural gas which was relatively abundant a couple years ago in a way and cheap, but a lot of -- a lot of countries, a lot of facilities are all moving to natural gas because it's the cleaner alternative in a way. And whether those will impact supplies, and mostly back the other way, it's something important to look at.

CHAIRPERSON KLEINMAN: So it might be something to suggest to the California Energy Commission. And I

believe UC has a multi-university unit as well that looks at the issues. And perhaps twist some arms to get more research done along those lines.

DR. KADO: There are some alternative fuels coming down the line that may have higher, as you indicated. For example, biodiesel has been brought up as one of those. But I'm not sure if those have been projected into these models right now. Good point.

CHAIRPERSON KLEINMAN: Could make next five-year cycle of standard setting more interesting.

DR. KADO: Yeah. There's also, you know, controls that are having an effect as well.

CHAIRPERSON KLEINMAN: Yeah.

Are there any more comments on chapters 1 through 4, or questions, Committee?

If not, let's start with Chapter 5.

And both Ralph and Laurie have looked at that.

ADVISORY COMMITTEE MEMBER DELFINO: Do you want me to go first?

CHAIRPERSON KLEINMAN: Sure. Use the microphone, please.

ADVISORY COMMITTEE MEMBER DELFINO: I found -- is it on?

Oh, okay. I just can't hear myself. Something in my ears.

Don't write that down.

I found it very thorough chapter. It was very informative, well written.

The first part was actually I think very important when looking particularly at the one-hour standards. We see in Figure 5.5 and Figure 5.6 on page 5-17, and then later on Table 5.4, that if we're thinking about .18 ppm standard, it's not going to -- if the trends continue, we're not going to see any exceedances, maybe a few, because there's really only two. There's a couple in the South Coast Air Basin. So I'm not -- and I'll talk more about this in reference to the epidemiology studies.

So I guess the question is is -- you know, looking at this, what good would the .18 ppm standard? I think this was important in informing us as to the relevance of the .18 one-hour maximum ppb standard -- .18 ppm.

There was an assessment -- it must have taken a lot of work. I know how these exposure models can be difficult. It was an assessment of population averaged exposures of Californians using the inverse distance weighting mechanism method. And I just wanted to point out that this is likely to over-smooth true exposures, because you're relying on fixed site monitors that are cited for reasons other than determining a spatial

variability of NO2. And because of this, you get a lot of over-smoothing.

And in my review I gave a couple of references, one being Michael Jarrett's review of the literature, which really puts the IDW method in to clear perspective. There's nothing wrong with it. It's just you have to understand that you probably grossly underestimate many, many people's exposure.

So with that I thought the indoor -- the indoor NO2 section and the indoor versus personal was very comprehensive. It covered pretty much all the literature that's out there. Although there are new studies that should be published soon on the topic.

But the section on spacial variability of NO2 concentrations was limited. And I think this is very, very important -- it's a very important topic, one that of course you can't really address using central site monitors, and one in which is becoming increasingly recognized by the epidemiology studies that are finding that the central site data just is not adequate to characterize an individual's exposure to NO2.

So short of using a personal monitor, most of the newer studies, including the children's health study right here in California, my own studies, we're beginning to look at models that take into account sources, like

traffic. And in this section there was a mention of this here and there. But it really needed to be covered in much more detail just so that when we look at these regulations, we understand that whatever's measured at the central site is in many instances far less than what people are actually exposed to.

And there were two studies that were mentioned. One was Singer, which was the exposure modeling study for the East Bay children's asthma study. And they found that NO2 and NOx were around 60 and 100 percent higher than regional background levels at the schools.

There were three schools. Three schools were within 130 to 230 meters downwind from the freeway. In that case NO2 was 20 to 30 percent higher and NOx was 50 to 80 percent higher than regional levels.

There are several other papers that actually weren't mentioned in that section that are very important, one by June Wu doing an exposure assessment study for the children's health study. Found that within community variability of personal exposures -- this is using a model, then actual personal badges -- was highest for NO2, okay, compared to -- I think that was compared to black carbon and PM2.5. And that was 20 to 30 percent within community variability. So that would be generally in reference to one of the children's health study monitoring

locations. And that traffic was the major determinant. There was no surprise in that. The Europeans have really been way ahead of us in assessing the impact of traffic on NO2 exposure, and using NO2 to their advantage to model traffic-related exposures.

Another study that wasn't cited, perhaps because it's fairly new -- I think it came out this year in March -- and that's by Zev Ross/Paul English, looking at a very nice study done in San Diego County using land-use regression. And the group set out -- actually I think Ross did the analysis, but English really headed this up. The group set out a network of passive NO2 samplers cited in relation to various sources. And that really should be covered in great detail, because I think it really clearly shows the spatial variability, at least in San Diego, of NO2 and how -- and they did some comparisons to the ambient monitors as well. So it really puts this whole thing in perspective. And I would imagine if you went up to L.A. -- and I know the children's health study is doing some things in Long Beach in that regard -- and I think you'll find that it's even greater in the L.A. Basin and probably any urban core.

There was a -- in that section they had done a study some time ago using personal badges. And I thought it was interesting that Steve found that the highest

personal NO2 levels were for periods when the subjects were away from home, basically out traveling. So that brings in to the fold the importance of in-vehicle exposures. And I don't know -- I don't think that was covered in much detail. But I do think there are some good studies, including ones done by ARB, using in-vehicle NO2 monitors. And, again, it sort of -- we're getting away from the central site and looking at what people are really exposed to. And I don't know how you can regulate that except to regulate the sources.

That's basically it.

CHAIRPERSON KLEINMAN: Laurie.

Could you use the microphone.

ADVISORY COMMITTEE MEMBER CHESTNUT: Definitely.

Yeah, I think Ralph covered in much more detail one of the main questions and points I had about this chapter. So I'll just reiterate, I think the spatial variation question is a really important one, and especially what exposure levels might be in closer proximity to the traffic sources. And if there's more data on that available, as it sounds like there are, then I think that's something that should be talked about, because we're talking about bringing the central monitors down to some levels. But that's -- there's probably higher exposures at these closer sources.

So there will be some effect on that. But we need to understand that whole distribution to really understand what the population risk is.

I think the other thing interesting in this -- I'm getting enhanced allergy responses.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: We are near a freeway.

(Laughter.)

ADVISORY COMMITTEE MEMBER CHESTNUT: Well, I think the first thing of interest in looking at this chapter is: Well, where do we stand now with the ambient concentrations and what are the trends looking like? And I think -- yeah, it's clear that there's only limited exceedances of the new -- of the proposed standards, and it's primarily in the South Coast. And the trends there are already downward. So it looks like things are already in place to probably be meeting these proposed standards, of which it doesn't change what they should be, but it puts some context for us.

But just to quibble a little bit, I think Table 5-1 shows annual arithmetic means of NO2 concentrations. And it's not clear, but in looking from the staff report later, this looks like averages across the basins versus single monitors. But I think the standard would be measured at single monitors. So it looked like later

there's several -- sorry I'm having some trouble. There's several individual monitors that are above the 30 parts per billion in the South Coast.

Maybe I better stop there.

ADVISORY COMMITTEE MEMBER CHESTNUT: I just think it's important information that comes through later. It didn't show up here.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: I'd get you one of my cough drops, but I left them upstairs.

ADVISORY COMMITTEE MEMBER CHESTNUT: Actually I have something here.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Well, you know, one thing that I just want to comment on, which is rather apparent, is a lot of the standards especially considered air quality and air pollution control over the last 50 years has looked at really regional pollutants and their impacts. And there's a great deal more of looking now at -- and the monitoring networks have been set up with central site monitors. And specifically the monitoring network was set up so we wouldn't look at -- wouldn't be affected by nearby sources, things like that.

But the question is -- in fact this is a good one maybe for BART as well is do the health studies -- are

they -- what kind of data are they using? Are they using central site data? I know a lot of what we're looking at, especially through the East Bay children's study, set up its own monitoring system itself. So it did rely on central site. But that would be I think important for how you interpret the results of the -- at least the -- more of the epi studies rather than control studies.

ADVISORY COMMITTEE MEMBER CHESTNUT: I think it also brings in that the epidemiology studies using a central site hopefully at best are tracking that distribution across the population. So you aren't necessarily missing those higher exposures. But to the extent that there's just a lot more noise in that central monitor as a measure of the population's exposure, that could result in less chance of finding an effect in an epidemiology study that's used in central monitored data. So that's an important I think point that needs to come through on that spatial variability.

CHAIRPERSON KLEINMAN: Another place where that comes into play is when you start to look at the health relationship in the dose response. Some of the variation from city to city to city may actually have something more to do with the spatial distributions as opposed to the difference in sensitivity to populations or toxicity. And I think it would be worthwhile to at least acknowledge

that point, you know, in the appropriate sections. As well as there were some of the public comments, which we'll get to tomorrow, that actually deal with that variability in slope factor. And I think part of the reason for it might be this kind of spatial variability.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, I agree. That's a key issue in interpreting the end-map studies too, by the way, where they're looking at long-range transport versus within city spatial variability. And they tend to miss -- they tend to miss associations in Los Angeles probably for that reason and never have considered that.

MR. LARSEN: Can I make a comment?

CHAIRPERSON KLEINMAN: Sure, go ahead.

MR. LARSEN: Yeah, Larry Larsen again. A very quick comment on the table that you mentioned.

The table that was prepared that you noted the very low concentrations for an annual average on was done inadvertently. It was meant to actually represent the highest site within the basin. But it did in fact average all the hours for all the sites within each basin. And a replacement table for that I believe is -- has already been prepared? Okay.

Another aspect though of an annual standard and how we do attainment designations with respect to an

annual standard, it is our practice now with respect to all of the annual standards we have in place to again look at three years, where the annual average is done separately for each of the three years for each site. And the highest year, not the average of the three years, but the maximum of the three years at each site would be the characterization that we use. And, again, the highest site within a region would be used to determine the attainment status of the region itself.

CHAIRPERSON KLEINMAN: One thing to educate me more than anything else, on Table 5.3 on 515, I didn't quite understand how the statewide maximum can be more than the maximum from any of the other sites. I'm sure there's a logical reason for this.

MR. LARSEN: Mathematically I'd be very hard-pressed to defend that point.

(Laughter.)

CHAIRPERSON KLEINMAN: Whoops.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Maybe those air basins not mentioned had really high values. But I think that's something we have to look at.

CHAIRPERSON KLEINMAN: Okay. Yeah, I was just wondering, because it's picked up on Figure 5-4 on page 514 and then here. And it just seemed like a mismatch.

There might -- yeah, it may Mathematically be right. But I just think it needs --

MR. LARSEN: Yeah, we'll have to take a look at that. I do not know this table.

CHAIRPERSON KLEINMAN: Okay. Are there any other comments relevant to this chapter?

We do have some fairly extensive, you know, written comments that we'll be, you know, putting together, and that will be part of our report. So hopefully we haven't missed anything.

So I guess at this point we can move on to the controlled human exposure studies.

And Dr. Adams would like to go first on this.

ADVISORY COMMITTEE MEMBER ADAMS: Thanks very much. I've prepared a three-page document for our Chair, of which I'd like to talk about a third of that at this particular point, and then defer to my fellow members, Russ Sherwin and Dean Sheppard.

A detailed presentation and analysis of controlled human exposure studies by the staff is given in Chapter 6 of the technical support document. I find the analysis to be thorough and complete. It is well organized, dealing with appropriate topics in logical order in combination with presentations of essential detail in the text. The latter is supplemented by seven

tables in the appendix that specify each important study and a summary of important details.

Data from studies of healthy adults, almost all of whom were young, exposed to NO2 concentrations up to 4 parts per million for several hours with or without exercise shows that they do not experience symptoms, changes in pulmonary function, or increased airway resistance.

However, exposures to NO2 in the range of 1.5 to 2 parts per million has been found to cause small statistically significant effects on airway responsiveness in healthy individuals.

Few studies have examined responses in healthy elderly subjects. Although the results in one study suggest that there may be a significant decrease in FEV1 response in older smokers exposed to 0.3 parts per million NO2 for several hours.

A summary comparison of responses to NO2 exposure in healthy adults, again almost all of whom were young, and asthmatics is given in Table 6-7.

Overall the clinical studies of asthmatics suggests that NO2 exposure at or near the current 0.25 part per million one-hour standard enhances the response to an allergen in those individuals with allergic asthma. Observed responses include decrements in lung function,

increased inflammatory response in airways, and evidence of activation of eosinophils. Although these responses were not observed in all studies of asthmatics.

However, for some asthmatics exposure to NO2 at levels near the current one-hour standard will very likely experience increased airway reactivity. As shown in Table 6-3, reduced lung function in COPD patients has also been observed when they were exposed to NO2 at the current 0.25 one-hour standard.

The clinical significance of increased airway reactivity after NO2 exposures in individuals with preexisting respiratory disease is the potential for a flare-up or exacerbation of their underlying respiratory disease.

The question of asthmatic significant differences in some studies and not in others -- remember this -- because asthmatics vary substantially in the severity of their disease, study differences may well be due to this factor rather than statistical chance per se.

You follow what I'm saying there?

I've prepared a response to the questions raised by our Chair in his e-mail. I'll share though just one of these questions with you at this particular point germane to what my comments previously have alluded to.

Are the estimated effects suggested by controlled

exposure studies sufficiently adverse to be a basis for short-term standard?

I believe so, for individuals identified above. Adverse clinical effects, although only observed in a limited portion of the adult population, were observed at levels as low as 0.25 parts per million. Lowering the one-hour standard to 0.18 parts per million would appear to provide a reasonable margin of safety.

And did you want me to respond to questions now or to pass on the microphone?

CHAIRPERSON KLEINMAN: No, I think we can just go ahead and pass on the microphone. I think the response to the questions is in writing, and we'll pass those on to staff.

ADVISORY COMMITTEE MEMBER SHERWIN: Well, I have to start off by saying that the key to my talk is an old story. And the old story is the grand M, capital M, which says all of our health effects have been related to three big areas: Mortality, morbidity -- and I've introduced a term "morbility," because what we're worried about more than anything else, as pathologists anyway, is what's below the surface.

We see, just like the iceberg, a big proportion of disease below as opposed to what's above. And asthma, as just mentioned, is one of the great examples of this,

because it's such a mixture of diseases. I can't go into the studies we're doing right now, but they're young people. And I've been impressed by the individual variability and the 15 percent severity in a group of, you know, ostensibly, sampled population: Young kids dying in motor vehicle accidents and homicide. So they have severe asthma.

Only a few of them did we elicit any kind of a history. But of course, again, you see, we have the same problems that you have with the clinical and tox. And, that is, we want those kinds of cases, sudden deaths, so they don't get complicated by being hospitalized. But then we can't get good histories because they're violent deaths and we have to depend upon next of kin, and it's not the most reliable.

But we did get some information. And, surprisingly, most of the information we got seemed to be environmental influences, kids who -- students who work with grinding, dust, painting, dusty atmospheres of sorts, occupational. Wood, for example. Well, what does this mean? It means that your asthma is a tremendous mixture. There are variations in eosinophilia. And you may be aware that not all asthmatics have eosinophia.

And at the same time let me mention that our young kids, 4 of whom of some 69 had a history of the ones

we get inflammation on, had a history of asthma. But not one case did we have classical pathologic asthma. Horrendous number of eosinophils. Horrendous amounts of bronchiolitis and chronic bronchitis and chronic glandular bronchitis. So it's all mix. And we get into that other thing called emphysema, asthma, chronic bronchitis, bronciolitis, and we don't know much about how to separate these sharply.

So when you start talking about testing groups for asthma and testing them for emphysema, COPD, whatever that is -- and while I mention that, let me tell you a curio which just came across my desk and, that is, emphysema's the fourth leading cause of death nationally now. I think it was 1952 or something like that when California first recognized emphysema as a disease. So all of a sudden -- well, it's something very strange going on. It may be the third leading cause of death according to the latest information. But the information I thought was really curious is there are some places where emphysema already is the third leading cause of death, in the Los Angeles County. And of all things, Antelope Valley has emphysema as its leading -- as its second leading cause of death. Now, why? Well, I don't know. I'm going to leave it up to you people to give me some answers on that.

But they have a lot of dust storms in Owens Valley and Antelope Valley. And that may be some of your answers.

But the message that comes out of this is, one, what a difficult pathological job it is to make a diagnosis; and clinically and testing it must be equally or worse. So that's a critical thing.

The second thing is: How do you measure emphysema? So we have studies on COPD, which you do have. Henry Gong I think did a study on COPD. But he didn't find any functional -- no -- as the critics will say, there's no symptoms, no signs. And so it doesn't mean anything. But the hallmark on emphysema is vanishing lung disease.

And, incidentally, I should have prefaced my remarks by saying I thought the reviews were excellent, I thought it was a great job. And the only reservation I had was I thought there should be more attention paid to morbility. In other words, the idea of: How do you measure some of these things?

And getting back to the emphysema, if the hallmark of emphysema is vanishing lung disease -- it's a silent disease. There's no -- I don't know of any pulmonary function. I think the argument I always give when I come to a chess meeting is you can lose 25 percent

of your lung before your PFTs become positive first test. So why would you necessarily expect the function test to be bad? Or turn it around the other way, it probably is so bad that your incremental change is going to be small. So that becomes a critical thing.

We have no technology to measure depletion. A person who has never seen a physician, who gets short of breath -- and I mentioned this, I'm sure, before -- has lost probably 70 percent of his or her lung irreversibly with nobody knowing about it. So that is one of the problems that we're up against.

So somehow or another the word -- the phrase "best judgment assessment" comes in. And that says that I go entirely along with your recommendations, because I feel as though there has to be a margin. And what you have picked up above the surface, I am sure is magnified manyfold below the surface. So I'm strongly in support of the recommendation.

Let me mention some other areas I think would warrant attention, maybe. And you can think about it.

There was a recent study done -- and you mentioned it -- it was Wellenius who did the study. It's the first study I know of where they showed a relationship of air pollution to congestive heart failure. And they did it with particulate. But we have been doing studies,

and others, with leaky lungs from NO2. And we've done a number of studies at .4, .5, .6. But the .4 definitely had statistical significance, a leaky lung exposed to .4 NO2, in animals of course.

And what does this mean? Well, it means that these people are going to be more susceptible to infection. They're going to be more susceptible to thrombotic phenomenon. And it's the only -- you mentioned the Richter's report on facilitation metas -- I think that's extremely important. I would not -- I would recommend that every operating room make sure that the air is really cleaned up. Because if NO2 were to arise in an operating room, it would -- it would facilitate the seating of cancer cells. Seating of cancer -- cancers metastasize in some people and not in others. Why is that? And we don't know.

But one of the factors is seating. And in seating comes endothelial damage. And one thing that probably warrants a lot more attention is endothelin, nitric oxide effects on endothin. Cigarette smoke has been shown to affect the endothelium. Nobody's ever done the NO2 studies. Somebody should be putting in a little reminder saying that if we ever do the NO2 studies, we'd probably come up with endothelial damage, with perturbations of nitric oxide that endo -- and the

endothelin system in the lung.

Butt the most important thing is in Wellenius' study is you could wind up with more congestive heart failure. We're not talking about the heart. We're talking about pulmonary edema. The real problem of congestive heart failure is leaky lungs, which is exactly what we were working on.

Leaky lungs, as I mentioned, are -- well, we'll be prone to a lot of diseases, infection being one. Instead of going into congestive heart failure, some of these people are going to get infections with leaky lungs, and you won't know it.

Well, so much for that part. Let me go on to -- let's see -- Wellenius, yeah, see, he had a comment which I thought would be worth repeating, and I thought that I would quote it for you. He said, "Triggering by particulate exposure" -- and I would just substitute, "Triggering by nitrogen dioxide exposure of acute decompensation in patients with congestive heart failure has not been evaluated in a systematic manner." Well, I don't know if anybody's ever done that with NO2.

Okay. So that's an important thing.

A strict aside, which is something I know nothing about, but I'm -- rather than throwing in one of the commentaries, I thought I'd mention it here. I saw an

interesting article on the subject domain approach to assessment. I know nothing about it. But the quote that caught my attention was: "School children's risk of illness absence were significantly related to acute exposures to nitrogen dioxide and nitrogen oxides." By contrast, the authors could not detect significant associations between air pollution and school children's absenteeism using time domain approaches.

However, the bottom line was that when they used subject domain, you know, they found the solution to the problem -- they got the results. I don't know if that has any meaning, but I thought that I would mention that it intrigued me.

We talked about our leaky lung. We come down to an area -- again, I am seeing young people all the way up from infancy on chronic and acute bronchiolitis. It seems to be ubiquitous. I don't think I've seen any young person who didn't have some bronchiolitis. I mean it shouldn't be surprising, because how many of us have a flu episode, we're coughing, we're sneezing. So underneath that clinical sneeze and cough is bronchiolitis. Every one of these young people I look at has bronchiolitis. And one out of four has severe bronchialitis -- severe -- and associated with a lot of other things which I won't go into.

But at any rate, it tells us that more work with a fetus might be useful. And as I went through your studies where you talked about developing lung and the John Peters group and so forth, I came across a -- I don't know whether you mentioned it or not. You had some references in the technical support and some in your staff report, and they weren't all redundant. Probably all -- Wellenius was not in the technical support document, and I think it probably should be, along with Peters' work, just to have completeness.

Whether LIU is in there, I don't know. But I was intrigued with their association between maturnal exposure to ambient air pollutant during pregnancy and fetal growth restriction in utero, and the comment, "A 20 parts per billion increase in NO2 in the first, second and third trimesters" -- and they also went into the PM10, the 10 microgram increase in PM10 -- "were associated with increased risk of IUGR" -- that's interuterine growth restriction. "And our findings add to the emerging body of evidence that exposure to relatively low levels of ambient air pollutants in urban areas during pregnancy is associated with adverse effects on fetal growth."

So I know you covered a lot of this, but I thought that that may warrant emphasis.

One of the last two is on the susceptible

populations. And as I mentioned, since all of the young people we deal with have bronchiolitis -- and, incidentally, every adult has some degree of emphysema, every adult. You're on your way out of lung reserve early on. It's just unfortunate. The big question is is to -- and if somebody said with air pollution, NO2, "What answer do you want?", I would say, "I'd like to know what the rate of lung reserve depletion is with and without NO2 exposure. Do I lose lung faster in Los Angeles?" And, incidentally, I may lose it faster in Miami or Hawaii with all the molds around. We originally did our study with a comparison with Los Angeles and Miami and found that we had probably -- well, I can't come to any conclusions, but I can tell you that I'm looking at more eosinophilia in Miami than I am in Los Angeles. And they both have a lot. And I suspect the humidity and the molds. And EPA turned me away from Honolulu. I wanted to do that study.

(Laughter.)

ADVISORY COMMITTEE MEMBER SHERWIN: But they have more molds -- they have more asthma than anybody else does. "Oh, no, you can't do your study." What a great place to compare your studies.

But I was surprised to learn that their sugar cane, for example, has so much fungus, five billion spores to every gram of bagasse that -- and it's always up in the

air. So that pristine area is not very pristine. But the moral that I'm trying to bring in is that we have susceptible populations all around. Who would have expected you're going to be in a susceptible area if you went to Hawaii?

CHAIRPERSON KLEINMAN: Well, if you look at some of the stuff that Colin Solomon did where they were looking at allergy after NO2 exposures, you know, presenting allergens, they were finding results too.

ADVISORY COMMITTEE MEMBER SHERWIN: Well, I -- that was relatively new information to me, and I didn't know that earlier and a lot of other people didn't know that.

CHAIRPERSON KLEINMAN: Right.

ADVISORY COMMITTEE MEMBER SHERWIN: Anyway, the bottom line to what I'm trying to raise is that in your technical support data you talk about susceptible populations. Well, it's a very limited discussion. And I -- you know, obviously there's limitations to what you can do. Just as the exclusion of some reports have to be left out, I don't fault the report review for leaving out some of our -- on leakage study, because some of the studies, .5, are pretty high. But nobody's done -- .4 was our lowest. Nobody's done anything lower. We never got around to doing any lower studies.

But at my rate, it would be nice to put a list in there, add to the support data a real listing of who are susceptible. That would have carried in pregnancy. It carried in the elderly of course. It would carry in the frequency of respiratory disease in young kids. It was very high. The frequency of a lot of infections in young people.

But above all, it would wind up showing that we actually do have a predominance of susceptible people. The last report I ever saw a study was one by Gladys Meade by the American Lung Association. I have it somewhere, but I couldn't put my hands on it. And I think she came up with something like 55 percent or 56 percent of the population was -- any urban population, would be in the especially susceptible group. So I would certainly like to see a listing -- an update of that.

And the last of all, I think it might be worthwhile also putting in here a definition of adverse health effect. You alluded to it in your report that it's difficult to define, difficult to measure, and difficult -- but a lot of people that put a lot of time, and ATA published -- I was asked to be a part of it. But I objected to something and dropped out. I didn't feel at the first one that a function test was okay if you didn't do hard work. If you had altered function but you didn't

do hard work, then it wasn't adverse. It was only adverse if you did hard work.

And you mentioned earlier about -- what was that, those young people pushing a lawn mower that was motorized? And you were surprised to see some of them with their blood pressure go -- pulse rate go up.

So the moral of the story is is that it'd be awfully nice to have a good definition of adverse health effect. And I would hope that that definition would cover subclinical disease and the loss of reserve. And when you do that and then draw attention to what's below the surface, then you're recommendations will receive phenomenal -- to me extraordinarily strong support, because what we don't know, what the technology hasn't yet given us, is already being pointed to by what you have found and summarized.

CHAIRPERSON KLEINMAN: Okay. Thank you.

Dean.

ADVISORY COMMITTEE MEMBER SHEPPARD: Yeah. So I think you did a very nice job on a difficult field actually, the human exposure studies for NO2. But of all the criteria pollutants, NO2 is the one where the data are most confusing, I think. And you did a reasonable job of summarizing some of the confusing aspects of the data. So I really don't have any major criticisms.

I guess I had a few sort of style points maybe that it would probably -- you could probably make a stronger case just focusing on the studies where there were statistically significant differences. You know, the reason we use statistical analysis is to try to prevent making specious -- drawing specious conclusions. And so I think I probably wouldn't put so much emphasis on studies that had something that would -- you know, showed a trend but it wasn't statistically significant or there was a close to statistical significance. You know, I think there are enough statistically significant effects that you could really focus principally on those.

I think, you know, I might in some areas be a little bit more circumspect in interpresentation. I think mostly you were. So you several times focused on the studies where there were a few people who had a big effect and then -- you know, for 3 out of 15 or 3 out of 20. I think it's okay to mention those. But it'd probably be good to, you know, always say that these results suggest that a possibility that some people might be more susceptible. Occasionally you kind of maybe went over the line a little bit in saying that the results consistently showed that there was a group of people who had extreme sensitivity. And I think -- but that's one possible interpretation. It might be correct.

But NO2 is tough, because the results have been somewhat more inconsistent than with other pollutants. And so, you know, it could always give you some pause. I think you mostly did a good job of capturing that confusion.

I have some really minor little criticisms that I can send -- or suggestions for typos and things I can send to Mike. But I think overall you did a nice job with a pretty tough field.

CHAIRPERSON KLEINMAN: Great.

One of the things that seemed to come out of the data, and especially in Table 6-2, is that there were a greater proportion of studies done at rest that had significant findings, whereas many of the studies done at levels of exercise in protocol seem to have trends but not statistically significant responses.

And I was wondering -- and perhaps this is more appropriate for our VMDs on the panel -- the effect of exercise on variability in responses of people with asthma. It seems that the error bars tend to get a lot bigger on those. I wasn't quite sure in looking at the table, because it is a little confusing because there's so many data points in there, but whether it would be worthwhile, you know, making some comment about exercise induced variation and variability as one of the

confounders in these kinds of studies.

ADVISORY COMMITTEE MEMBER SHEPPARD: Mike, I'm not sure that really adequately explains the observations, because many of the studies that we're talking about were increases in airway responsiveness that were measured several hours after the exposure. So it's hard to understand why exercise would increase the variability several -- I mean you can imagine why exercise might increase the variability measured right away, because there's exercise induced bronchoconstriction. But five hours, six hours later when airway responsiveness or allergen responses were measured, it's hard for me to think of a biologically plausible reason why exercise would increase variability.

ADVISORY COMMITTEE MEMBER DELFINO: Can I comment?

CHAIRPERSON KLEINMAN: Sure.

ADVISORY COMMITTEE MEMBER DELFINO: There's a mounting evidence now that exercise induces more than just bronchoconstriction in asthmatics, that in fact it enhances inflammation as well. You see in exercise neutrophilic infiltration into the airways, activation of cytokines and chemokines. And that would be expected to have an effect hours later, if not even 24 hours later. So I think there's good experimental evidence that that's

the case.

CHAIRPERSON KLEINMAN: In that case, it probably would be worthwhile to make some mention of that, you know, as part of --

ADVISORY COMMITTEE MEMBER DELFINO: I can provide some references. We're doing a study like that right now. So bringing some of our asthma panelists into the lab and doing exercise challenges and measuring peripheral neutrophils and other markers. So it's very -- you know, with kids you can't go in and do bronchial washings. But there's an experimental background all over that.

DR. KIM: Well, I think that maybe point to separate out, that some of the studies on looking at enhanced allergic response of the controlled human exposure studies have been -- the majority of them have been done at rest. And I think the issue about exercise versus rest were findings related just to airway reactivity. And there was a following -- sort of pooled analysis to try to tease that out. And I think it's difficult. I haven't read anything really to address that.

I think most of those earlier studies on airway reactivity are done relatively soon after the exposures. It's not -- because they're not looking at sort of an early or a late phase response related to allergy

challenge. But maybe, Dr. Sheppard -- and in that sort of situation, say, within -- some of them were done I think an hour after exposure, some of the airway reactivity studies. Would you expect then for mild asthmatics to see that bronchoconstriction at that time?

ADVISORY COMMITTEE MEMBER SHEPPARD: Well, usually the bronchoconstrictors --

DR. KIM: For airway reactivity increase.

ADVISORY COMMITTEE MEMBER SHEPPARD: I think it's pretty controversial whether exercise would be expected to increase airway reactivity. I mean measuring leukocytes in the blood stream after exercise is a response to stress hormones, I would presume. But what's really relevant is airway responses. I'm not aware of much evidence that there's an increase in airway responsiveness an hour after exercise. You know, there's an initial bronchoconstrictor response to exercise, which is usually relatively transient.

I think it's -- you know, you did an excellent job, because it's a very confusing literature. It would have been obviously much nicer if we saw a consistent concentration, dependent responses across studies. But that's just not the way the literature is.

There's actually I guess maybe one other just sort of summary point about that, is what you did stress,

which I think maybe, you know, is the point that needs the most emphasis, is that there does appear to at least be a biologically plausible coherent body of information, you know, that fits inflammatory responses in the airways in people and increases in allergen responses and in airway responsiveness. You know, that kind of makes some sense. So I think the biologic coherence of the data are probably the most convincing point, rather than actually the coherence among -- you know, among the individual studies addressing any one of the particular endpoints.

You did get at that nicely. But that's probably the point that really bears the most emphasis.

CHAIRPERSON KLEINMAN: Dr. Plopper.

ADVISORY COMMITTEE MEMBER PLOPPER: Yeah, I just wanted to second the previous comments about the quality of this chapter. I think it's great. And as I was reading it, I wanted to share something that concerned me. And that was that you -- because you outlined it so well, it's easy to see how variable these exposure studies are. And it seems to me, if I'm not correct, that some of these studies are for 30 minutes, some of them will go up to 6 hours, some are for 1 day, some are as many as 4 days; correct?

And the measurements are sometime immediately after the exposure or 24 hours later. Okay.

So what bothered me was then when I look back at Chapter 5 to figure out, okay, is there anything in California that's going to put one of these people at risk? And what I don't understand is -- could somebody maybe -- somewhere in here there needs to be some, seems to me, because -- actually because of the e-mail -- invention of e-mail, I now get these kind of questions all the time from the public and I don't have an answer for them. But you're the expert, so you're going to help me with this.

So how would you look at one of these -- this Chapter 5 and tell me what the response is going to be? Is there a site of risk? Because these -- the way these things are measured at the moment, there is no -- if there was an exposure, say, .25 for 30 minutes, would it get -- the same information would be available to an epidemiologist, say, as if that exposure had been for 6 hours; is that correct? It would be the same information. You had no way of discriminating that; that's correct?

Well, it looks like that those little peaks may be just as important and the 6 hour.

And the other concern is that our -- this comes from doing these things to animals. There's no PETA people here, but -- every time you do this, if you leave less than a 24-hour cycle, you compound it for three days,

then it changes and goes the other direction. Is there any way in here to be able to look at Chapter 5 and identify how many days in sequence an exposure exceeds a health risk? Because it only takes 30 minutes for 4 days. It could be a highly significant exposure and yet there's no way to identify that information in here.

And I think somewhere this has to be explained, because this chapter does such a nice job of delineating all of the different -- you can -- it's a crazy literature. But you can sit here. When you look through it, then you say, okay -- I get these kind of E-mails. And they say, "Well, just because our area is in attainment, does that mean it's healthy when the days look bad?" And I don't have an answer because I can't find the information that I can relate back to what I understand, which is what's in Chapter 6. And I think that's a really critical thing that needs to be in here, because the impression I get from the e-mails I get is that the public thinks you're trying to hide information. Okay?

Why would you average something over 12 months if it's once can make somebody sick because somebody reported that somewhere? And I don't -- I think you need to address that issue a little bit more specifically. And that was my main point.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: I think that's a really good suggestion. Chapter 5 on the exposure assessment that ARB put together I think really should cover some of these issues much more carefully.

There's two aspects of it. One, as you indicated from the epi studies -- by the way this is Ostro from OEHHA -- from the epi studies it's really hard to discern what the exposure -- relevant exposure periods are. But we do know from the epi studies and the exposure studies that being close to a major roadway -- and by that we define maybe 25,000 vehicles per day passing through, which is not huge. I mean there's highways an L.A. where it'a a hundred thousand. So being within, say, 150 meters of a roadway with 25,000 gives you NO2 levels that are almost on an order of magnitude higher than background concentrations. So we should -- that should be clearly indicated in chapter 5. It's not only NO2, but it's also again ultrafines and carbon and so on. And so that's something that I think we need to include.

We mentioned a study by Zhu Z-h-u in Chapter 6. But I think that needs to be discussed as well in Chapter 5 where he goes through these things using L.A. Highway 710 as an example.

And the other aspect, I think you're right, is the descriptive statistics, rather than looking at

necessarily long-term averages or the single highest peak, I think there should be some indications even of 30-minute averages or what the distribution of annual -- or the one-hour averages are in some of these areas, particularly in southern California. Because you're totally right. Here we don't see many exceedances. But we know that everyday in urban areas near roadways people are going to be exposed to above .26 for 15 or 30 minutes. But there's nothing on that really well articulated. So I think we need that as a public information tool.

ADVISORY COMMITTEE MEMBER PLOPPER: Okay. Yeah, I just -- Dr. Kim's study's one that generated a lot of e-mail for me, because there were a separate set of monitors from the ones used for deciding attainment. And it showed that there was quite a heterogeneity there. And those heterogeneities were probably biologically relevant based on Chapter 6, but this document doesn't deal with those two issues.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: I have a question also for the AQAC members.

Dr. Sherwin gave us his suggestions on potentially sensitive individuals that aren't studied. I'm wondering from Dr. Sheppard and Adams, Dr. Plopper, if we have missed -- I don't think we've missed the

literature, but maybe we've missed conceptually other groups besides these asthmatics that may be sensitive that we should be at least thinking about, or ARB should be thinking about in terms of studies. If there's other potentially susceptible groups, we should think about that a little bit. So if there's any suggestions on other groups, I'd be interested in hearing that.

ADVISORY COMMITTEE MEMBER SHEPPARD: I guess the one group that you might think about mentioning is people who have immunosuppression for whatever reason, since, you know, you do bring out the point that there might be an effect of NO2 on susceptibility to respiratory infection. So that's a group I don't think's been studied, but, you know, probably's worthwhile mentioneding in the document.

ADVISORY COMMITTEE MEMBER PLOPPER: I think that even in this chapter it would be worth mentioning all the potential susceptible populations that limits because they're humans of trying to do an experimental study on, or out in children would be one, for sure, particularly if very young children. I know they mention children, but I think it needs to be a little more prominent in --

ADVISORY COMMITTEE MEMBER PLATZKER: In the comments that I'll share with you I outline pediatric populations that haven't been mentioned, starting with the fetus.

You know, the other point that I'll raise is -- has already been alluded to. Thirty years ago when this Committee addressed the issue of lead in fuel, we were set at an impasse in our deliberations until it became clear that if you lived within 500 yards of a freeway, your serum lead was two standard deviations above those who lived farther away. And that convinced us significantly that we had to remove lead from petroleum products.

For our air pollution data, at the present time we have no studies looking at populations who live next to freeways. In addition, they seem to be socioeconomically disadvantaged, except for one, and that's the -- UCLA has built faculty and fellow quarters right next to the freeway in Los Angeles, next to 405. But generally those populations are socioeconomically disadvantaged and should be studied.

And one other point that I should raise is that California's different. And I'll give you an example from pediatric illness. In cystic fibrosis nationally 5.7 percent of the CF patients are Hispanic. At our center in California we have 50 percent Hispanic, and the disease is different. It's different than the rest of the nation; it's more severe, and especially the lung disease. Now, part of this may be attributed to the unique mutations. Hispanics in California have 11 unique mutations of CFTR

which are responsible for their CF. However, you can't exclude that the environment that they breathe is different than those, for example, in Boston or New York. And that may be a factor as well, but we have no studies.

If I can just allude a little bit to CF. Very unique population, because every CF patient diagnosed is placed in a registry, and there's huge amount of data in that registry, which is on line and we have access to it. For example, four times a year pulmonary function data. Also its inflammatory markers are included in the data, frequency of hospitalization and exacerbation, and even the organisms they carry. This would be a fruitful population for study, especially if you could use as control for California CF, CF patients from other states. A very interesting group, because the data is there, and it's data that they have from diagnosis in perpetuity.

Can I make another comment about -- there was a discussing of airway reactivity and exercise induced bronchospasm. And one of the difficulties in studying that in pediatrics is about 10 percent of children -- we're talking about young children -- who have no history of reactive airways disease or asthma do have exercise-induced bronchospasm. You can produce it in -- so that is sort of an interesting side effect and it should be mentioned.

ADVISORY COMMITTEE MEMBER PLOPPER: I just wanted to follow up again on Arnold's comment, is that on page 6-23 it does -- it needs to say exactly what he just said, because it talks about children that are -- the youngest is age 8. And our experience from animal studies would say that's too old. But what -- it needs to have a statement here that says, "These are the populations of children that are missing." And that's the pediatric population, the very young ones. That's what I think. I mean -- you know, because that's going to be a critical population. You mention it other places, but you don't point out that there's -- that the data that's there is only for older children. And those children are pretty -- have pretty mature lungs by that point.

CHAIRPERSON KLEINMAN: Okay. Well, if there are no other comments on these chapters at this point, I think this would be an appropriate time to break for lunch. And we'll reconvene at 1:30.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON KLEINMAN: We're starting again. I know we're starting a little bit behind. But we're up to the most important and interesting part of the program. We get to grill Bart on epidemiology.

(Laughter.)

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: So, Mike, would you like us to go over that exposure table right now or --

CHAIRPERSON KLEINMAN: Sure.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: So, Larry, why don't you go and explain the table.

MR. LARSEN: Sure. This is Larry Larsen again.

The table that was in question is page 5-15 in the technical support document here. And it's table 5.3.

The question came up, when you go to the right-most column, Statewide: How could it be that the statewide maximum is higher than any of the values in the rows? And this really -- I told Richard Bode here that I went and had a cup of coffee and it came to me. So this is an exercise not in new math; it's a basic kind of thing.

But the story goes this way: Consider the South Coast number for January, .092. That does not represent a single site. What it says is for January you would take

the highest value on any given day for January and average the highest values. They might be a different site on different days.

Now, keep that same principle in mind that go to Statewide. Statewide it says no matter where in the state it happened to be, pick the highest state. So the statewide is actually taking maximums from different air basins throughout the month of January and averaging those January values together. That's the math behind it. It's not explicitly stated that way, so at least this should be clarified.

CHAIRPERSON KLEINMAN: Okay. Thank you.

There was also another question -- we put it in the written part of the notes -- that the note at the bottom of the table was a little confusing. But we can deal with that some other time.

MR. LARSEN: Okay.

CHAIRPERSON KLEINMAN: That just needs to be clarified, I think.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: We'll clarify it.

CHAIRPERSON KLEINMAN: Okay. So I think we'll start on the epidemiology. And we'll start with Ralph Delfino again.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, I'd say

overall it's a very comprehensive review and incredibly detailed, covering many, many studies. And it points out a lot of the weaknesses of course with the epidemiologic studies. And of course one of those weaknesses is the fact that all of these studies -- nearly all of these studies use central site exposures where NO2 is measured simultaneously with other criteria pollutants like particle mass and ozone. And so that induces a high correlation between the pollutants and it makes it difficult to separate effects out in the epidemiologic regressions.

But I don't -- I don't think that takes away from the importance of NO2 being representative of many other pollutants that aren't regulated, including a plethora of organic compounds, other unregulated gases, semi-volatile and volatile organic compounds that, while they're regulated, aren't routinely monitored.

And I would just have to say that I think the situation for NO2 is analogous in many ways to particle mass concentrations that are -- like PM2.5, that are regulated. PM2.5 is just particle mass. And depending on where you are spatially and temporally, it can represent a whole host of different components. And so I don't -- I know that the focus on the Regulation of NO2 has been traditionally on NO2 as the molecule. But that doesn't

necessarily have to be, particularly given the fact as described in the exposure assessment section, Chapter 5, that the spatial variability of NO2 is considerable, particularly due to higher concentrations in proximity to vehicular sources.

So I thought the discussion of the time series study was fun. And for the studies that did look at NO2 and did two pollutant models, for many of them I thought the associations for NO2 were remarkably robust, almost unexpectedly so, even in the face of significant particle association. So I think, again, you need to take that with a grain of salt and use that as an indication that NO2 is probably representing something that particle mass isn't in some but not all of these studies.

I don't want to go out of sequence. I think panel studies were next, or cohort studies -- cohort studies.

I thought the conclusion on cohort studies was a little inaccurate. You know, to say there's little evidence, what -- yeah, what I think what you really mean is there aren't very many studies that have looked at long-term concentrations of NO2 and the instance of asthma, allergic rhinitis and atopic eczema. In fact, there are a couple of well designed and incredible studies done in Europe. One is a -- it's cross-sectional, yes,

but it is very high powered. And It showed -- this is Janssen, et al., that was reviewed -- it showed an association between NO2 and total IGE in positive skin prick tests for allergens. And I thought that was very informative. And it was consistent with a study I like, I think it's a remarkably informative study, by Kramer in Germany showing which -- this is what should have been actually presented -- showing that for the urban population, excluding the rural population, there was actually a linear association between NO2 and atopic sensitization NO2 and rhinitis -- allergic rhinitis in children.

And this NO2 actually was outdoor home NO2. So it wasn't ambient NO2. It wasn't indoor NO2. It was NO2 measured outside the door of each of these children's homes. And I think that's again particularly relevant to this spatial heterogeneity issue, that of course isn't addressed from the ambient data.

I have a bunch of specific comments. None of them are terribly important. Just would like to see some better organization in terms of the tables, just, you know, by subject group and outcome would be a little bit clearer.

There was -- on lung function in asthmatic children, as you know, most of the studies are using peak

flow, which is fine. But it's well known that peak flow is not a great surrogate for FEV1. It really just -- and it can be quite variable, especially when measured in children, because it's more effort dependent. So FEV1 really is a better measure. And only until recently have panel studies started using FEV1. You reviewed one, moshammer, although that's a general population study and not asthmatic children, which remarkably did find inverse associations between NO2 and FEV1 deficits.

I have a study, and it's -- probably you missed it, one in Alpine. Actually there was a -- that measured FEV1 personal and ambient exposures. And we found ambient NO2 is inversely associated with FEV1. I don't think it's in the abstract, and that's probably why you missed it. It's in the text. We didn't measure personal NO2.

I will describe to you now a study that is not published yet. But I would be glad to send it to you once it's accepted. It's now under revision. I'm pretty sure it's going to be accepted. And I'll send that to Kleinman. He's a coauthor. And this is an asthma panel study that we conducted in Los Angeles, in Riverside, and the Whittier area of Los Angeles.

We followed 62 children, 45 of whom had ten daily exhale nitric oxide measurements done off line. And at the same time each child wore a personal air sampler for

realtime PM2.5 and a quartz filter measurements of elemental and organic carbon and 24-hour active personal NO2. And we have several papers validating those samplers.

We found a significant association between E and O in both personal and ambient NO2 and both personal and ambient elemental carbon in two pollutant models. So we put both personal NO2 in the same model with ambient NO2. Personal NO2 confounded the association of ambient NO2 with E and O.

But I have to say that there was a correlation -- there's a moderate correlation between personal and ambient NO2 of about .46. So this suggests -- I think this suggests that there are key sources, key pollutant sources that both personal and ambient NO2 share. And so -- and suggests that despite the exposure misclassification of ambient NO2 for personal exposure, that nevertheless the ambient NO2 probably represents some causal components that were related to exhaled and out.

And for those of you who don't know, this is a -- exhaled and O -- E and O is a marker of airway -- is believed to be a good bio-marker of airway inflammation, one of the hallmarks of asthma.

So more interesting stuff with that study. We also found that in two pollutant models the E and O

association with personal NO2 was independent of a significant association with personal PM2.5. And it was also independent of -- well, the ambient NO2 -- okay, looking at just the ambient side, the association of ambient NO2 with E and O was independent of ambient PM2.5. And in fact ambient NO2 confounded ambient PM2.5. So it was a more robust parameter.

The other thing is we had ambient elemental carbon and ambient NO2 again were associated with E and O. And in two pollutant models they confounded each other. So there was no evidence that one versus the other was better. So they both were basically carrying the same sort of signal, likely a traffic or vehicular source related signal.

This was not so for personal NO2 and elemental carbon. They were independent of each other largely, with some small decrease in the personal NO2 signal when co-regressed with personnel elemental carbon.

So that's kind of it in a nutshell. So I think you can understand that this study will actually give you a lot of information about the effects of NO2 at both personal and the ambient level in the face of associations with other pollutant measurements, including PM2.5 and carbonaceous aerosols. So I will send that to -- well, Michael will have of course the revised manuscript. And

then when accepted, we'll send it on to you guys, if that's okay. Do you think that's okay?

CHAIRPERSON KLEINMAN: Um-hmm.

ADVISORY COMMITTEE MEMBER DELFINO: I need to get back to where I was.

So one of the things that -- one of the things I was a little concerned with was the one-hour standard of .18 ppm and how that related to the epidemiologic studies of acute exposure response relationships. Because I think that's where it's relevant, okay, the one hour maximum. Because a susceptible child or a susceptible elderly person with heart disease, they're going to be exposed to these peaks acutely and then have acute outcomes. And I think that's probably the purpose of the one-hour maximum standard, is to protect people against these acute exposure response effects.

And so it would be important to put that in a context, particularly of the panel studies, but also of the other studies looking at acute effects, by showing us in those tables the maximums -- more would be better, but at least show the maximum NO2 instead of just the mean. Because if you look at the mean actually, they're all, you know, 20 to 50 ppb's. So far less than 180. And I can tell you, I don't think any of our data suggests that -- in Riverside and Whittier that we ever got to 180 ppb's in

any hour across the whole eight months of panel studies, but yet we're seeing associations. So I can't see how 180 ppb one-hour max would be protective for acute effects.

And not published or submitted or anything like that is we've presented ATS associations with FEV1 also in the same kit. So -- and we're going to be looking at symptoms and so on and so forth. And I'm sure -- and I'm sure we're going to find associations at levels that never even come close to 180 ppb's.

So I would like to see -- from what I understand, the .18 ppm standard is largely based on the clinical and tox studies. And I'm not sure that should necessarily be the case. It might be the case, okay, if you were saying we're only going to regulate NO2, the molecule, and what it does to the human lungs and so forth.

Bart.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah, let me just respond a little bit to that. And Janice can verify this.

In the clinical studies we tried to see whether there was an effect of -- or studies looking at longer duration, greater than one hour. And I think there was one or two studies that did try to look at multi-hour. And I think there was one positive and one negative.

DR. KIM: Right.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right.

So there's not much evidence from the clinical studies on those populations anyway that -- for those effects that they looked at that you see something greater than the first half an hour or an hour. They're like ozone where you do see the duration of exposure playing a big role.

So it could be the case that there's either two different types of effects and that these epi studies are not really representing one-hour exposure, that for the types of people that are impacting may be more moderate to severe asthmatics in a lot of the panels, that those longer term exposures matter for that group.

So it could still be consistent to have a .18 that's protective based on the clinical studies, and that the epi studies are really measuring and relating to the longer-term exposure.

ADVISORY COMMITTEE MEMBER DELFINO: The multi-hour and multi-day exposures.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, that's true. So there's really no clinical study that could probably, I don't know, ever mirror, that it wouldn't be

ethical to hold somebody that long in a chamber or whatever.

(Laughter.)

ADVISORY COMMITTEE MEMBER DELFINO: There was a figure you had that you gave us. Where is it? I thought that it ought actually be in the -- it was such a nice figure, I thought it -- oh, where the heck is it now?

ADVISORY COMMITTEE MEMBER PLOPPER: Page 4.

ADVISORY COMMITTEE MEMBER DELFINO: Sorry, I'm disorganizeed here.

You gave us too many pieces of paper.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: From my presentation or from --

ADVISORY COMMITTEE MEMBER DELFINO: Yes, from your presentation.

Here it is. Okay.

It's the one that shows key epidemiologic studies showing associations between NO2 and respiratory disease where you give the study number.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right.

ADVISORY COMMITTEE MEMBER DELFINO: I think it's an important slide, and it really supports the annual standard quite well. It ought to be in your document. And I don't know what the study number is. I was trying

to look that up. But I don't know that I can link the study number to the text. You know what I mean? So it might be an important slide to put in, and also note which study number 1 through 11 is.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: I think we will add it to the "Recommendations" chapter for sure.

ADVISORY COMMITTEE MEMBER DELFINO: Okay, yeah. I thought it was just a wonderful way of summarizing it quickly and showing quite clearly why .03 is a good level. In fact, it's sort of right in the middle of all of them. It just goes -- so there's some that -- there's some that seem to show associations at mean annual levels that are less than .3. So I would say that what you've chosen at .03 would be conservative given what you show in this particular figure.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: So, Bart, remind me. This slide is in the --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: No, it's not. We had a different slide in the staff report. We had different set of studies. So I think the new one will have this --

ADVISORY COMMITTEE MEMBER DELFINO: That's the one, yeah.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: -- rather than the one that we had in there.

ADVISORY COMMITTEE MEMBER DELFINO: You know, and when I'm -- for instance, the Gauderman study looking at lung growth where you see a decrease in predicted FEV1 -- that was a slide I think two slides before that.

Yeah, that one, you know, where you see this decrease in percent predicted FEV1 within the range of 25 or 28 to 40 ppb's. That's also very informative and very relevant to the standard that you're talking about. I mean this is a large cohort study. It's right here in California. It doesn't get much better than that.

And I guess that's it.

CHAIRPERSON KLEINMAN: Laurie.

ADVISORY COMMITTEE MEMBER CHESTNUT: Okay. I think the chapter does a really good job of explaining -- being really careful about explaining the limitations of the epidemiology literature. And it really gets to the crux of the problem here, is that it seems clear that there's an association of a whole range of health effects with a group of pollutants that NO2 is correlated with. But I just -- I don't see how this literature by itself can lead us to the conclusion that the NO2 is necessarily causing this.

So it poses a real significant regulatory problem

if that whole -- I mean if what you do to control NO2 is going to reduce that whole cluster, then fine. You know, if, for example, it's traffic, which it looks like it's probably a traffic-related emissions, and you reduce that whole set, then you've taken care of it.

But I think -- so I don't know how you would address this. The one way that is mentioned here, and I think what we have to do, is look at it across the chamber studies, the toxicology studies and the epidemiology studies to see if it's plausible that NO2 could be causing the types of health effects we see associated in the epidemiology literature. And here there does seem to be some plausible connections. We see stronger -- we see asthma-related things in the chamber studies and then we see a stronger association with respiratory-related illnesses in the epidemiology literature. I think -- and I'd be curious to hear what the toxicology experts in the group have to say, but the epidemiology studies showing the relationship between exposures and -- or NO2 concentrations and lung function development and then the toxicology studies that show effects in lung function development in animal models, that seems like a really interesting connection and really important piece of it.

And I think it's also -- if that's one of the mechanisms we have to realize in the epidemiology studies

of mortality, for example, we can't just look at -- the time series studies are not going to pick that up. If it's your exposures during your childhood that make you more vulnerable and may predispose you to premature mortality later in life, the time series studies of acute exposures are not going to reflect that.

And I think also even the cohort studies are going to have a tough time because it's the childhood exposures, and we haven't gotten that sophisticated in the cohort studies of linking the exposure to a certain time period.

But I think we're still left at a lot of uncertainties about what the -- what the actual quantitative standards should be.

So I think that's all I have on this section.

ADVISORY COMMITTEE MEMBER PLATZKER: The two previous speakers said a lot of what I was going to say. But my presentation is biased by my background. My career has really been focused on looking at whether early lung injury leads to lung disease as the child approaches adulthood. We've looked both at fetal lungs mainly in work on HIV vertically transmitted from mother to infant using the uninfected children as controls. And we've looked at a series of neonatal illnesses, respiratory illnesses and what the long-term consequences were.

In our studies we tended to look at mild disease rather than the worst disease in the newborn, and find that at eight years of age after alveolar development is complete the lung has a memory, and that even though these children -- that we selected children with no family history of allergy or asthma, that these children at 8 to 11 years of age have indeed evidence of chronic obstructive lung disease; that is, they tended to have enlarged residual volumes, they seemed to have lower mid-maximal flows than other children, and they also had -- and these studies included exercise challenge -- had exercise induced bronchospasm. So children represent an interesting model in how the lung deals with inflammatory injury.

And I think the weakness, if we feel that there is any weakness in the present environmental studies looking at NO2 and other pollutants, is that there wasn't foresight in putting together prospective studies to see whether injury that -- it could occur to the fetal lung, as happens with environmental tobacco smoke, for example, the impact of environmental tobacco smoke on lung development is more important in the fetus than postnatally, and the studies that we've done really don't look at that issue.

In addition, neonatal lung disease, such

respiratory distress syndrone, chronic lung disease of infancy, are inflammatory disorders. And while the acute inflammation is most marked in the first two years of age, this continues. And so we have neither lung function studies, which could have been performed, nor do we have inflammatory marker correlates of the lung inflammation that is existent in these studies. And I think this is a -- not anything to say negative about what you've done in putting together the resumé for this meeting, but rather a criticism of all the studies that have been done, and perhaps the lack of funding for adequate studies that would have given us this answer.

And then as -- there's another confounding variable. Many years ago Lynn Taussig showed that little boys are born with smaller airways than little girls. And it's the reason why in the first two years after birth boys tend to wheeze or cough much more than girls with respiratory illness. There's a crossover which occurs somewhere between two and four years of age. And as you know, in older children, wheeze and cough are more common in girls. It would be interesting to be able to define whether boys are more susceptible to early lung injury and perhaps chronic lung injury from inhaled pollutants than girls or really what the comparison would be.

Also, we know that there are certain racial

groups that tend to suffer greater from reactive airways disease in childhood. And certainly Hispanics and blacks are two of the groups that are most represented. If you look in Los Angeles County at our population, if you add the Hispanics to the blacks you have a majority of the population practically. And we have not looked at those issues.

And, finally -- the final thing I wanted to bring up is the issue that I brought up this morning about -- since we're talking about nitrogen dioxide an its group of -- or its associated pollutants, those go along freeways, and we have freeways that dot our state. And really there's a need for studies looking at populations who were born and raised near those freeways and comparing it to other areas of the state, the North Coast, which has very low problems with nitrogen dioxide, and perhaps Tahoe, which is also a rather lower area.

That's all I had to say.

CHAIRPERSON KLEINMAN: Anybody else have comments on Chapter 7?

ADVISORY COMMITTEE MEMBER PLOPPER: Yeah, I want to make another plea for a little bit more thorough explanation of what the exposure parameters were that were used in these studies. Because I'm having a tough time understanding whether they -- you know, when they take a

one-hour exposure and they averaged it, was it everyday, was it after one exposure? What does it mean? Like this chart up here, what about all the studies that you didn't put on this chart and what -- were their exposures different? We're all of the ones that are time series, were they all the same type of analysis of the exposure protocols? Just what are the alternatives ways that epidemiologists go about deciding what the exposure actually was? Given the constraints that you already outlined in Chapter 5, how did they get that kind of information and which ones -- how were their studies limited by what the data is there?

The other thing that concerns me is -- I didn't read anything in here, but I tend to be overwhelmed by the large number of studies here. I didn't see anything that talked about exposure history. And I think that was mentioned earlier. But if it's not in there, which I don't think most of them do, then it's really very difficult to understand when a study does not show a significant change, if that's just because the people that they picked for that study happened to be lifetime residents of a polluted environment, in which case from biological perspective they're going to be tolerant; and if they don't show any response, that's because they're already -- their lungs have been changed enough that

they're not responsive anymore.

That's not in here either. So a negative study doesn't mean that it didn't have an effect. It just means that the type of exposure that the epidemiologists were able to get data on to make their comparisons don't include an exposure history. And if they do, that's fine. But I don't believe most of them do. And I think that needs to be in here, because most people grow up in polluted environments. And I think that's already emphasized that the younger ages will have the major impact on how the lung develops. So that's going to make them tolerant.

I mean is that --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: That's a totally reasonable question. And I can try to give a quick answer. Or are you just suggesting that we try to document a little bit more?

ADVISORY COMMITTEE MEMBER PLOPPER: I'm just suggesting that somewhere in the -- you do a nice summary to begin with on other issues. It would be nice just to have something there: These are the types of exposure data that are used -- just data sets that are used, and try to relate that back to Chapter 5, which is how the data is collected, so that it's clear what -- the fact that -- I mean these issues about you can't have every

site. Well, that needs to be in here, because this is not every site.

So a lot of them -- how do the epidemiologists know that the noise in their data is just not because they don't have refined enough exposure protocols -- exposure data for each individual? Which they obviously don't based on what's in Chapter 5.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, for some of the studies that won't matter. In, for example, the time series studies, let's say, on asthma emergency room visits. So these are clearly short-term exposures. We're not talking about historical exposures. Although historical exposures could make kids more or less sensitive. But it's saying, given whatever previous exposures people have had, do we see a different effect relative to current daily changes? So for that type of study design, one of the nice advantages is that you don't need a lot of historical information. You're just saying whatever these people have been exposed to, do they have higher rates of asthma emergency room visits and hospitalization based on exposures today or two days ago or three days ago, whatever.

Now, for the long-term studies of course it would be of greater concern when you're looking at long-term exposure.

The L.A. cohort -- and I think Ralph would know this better than -- I'm not sure how far back they go. I think some of them go back to pretty early ages in terms of the measurements.

ADVISORY COMMITTEE MEMBER DELFINO: You mean the children's health study?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah. And actually a relevant paper recently published by McConnell this year or last year looking at traffic and asthma -- no actual measurements, this was just -- these were, you know, proximity to traffic estimates -- found that there was an association with asthma only among lifetime residents, okay? -- so that answers your exposure assessment issue -- versus those that had moved, and only among children with no family history of asthma.

It's also very interesting because asthma's an allergic disease, and when you have positive family history it's likely you have a lot of allergenic determinates of your asthma that might overwhelm any other association. But that's -- even though they didn't measure NO2, I think it's a good example of where things could go. I mean they could have used -- they could have used a Gaussian dispersion model estimate of NO2 in

relation to traffic and then called it NO2. But that's -- I think it's relevant.

ADVISORY COMMITTEE MEMBER PLOPPER: That's why I thought just something that was a general discussion in the beginning that explained those types of ways of going about collecting information would be important, and what's missing when it's not there.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: We can certainly cover that in more -- in some detail when we're describing the epi studies. I mean usually it's convenient samples and whatever's been collected on it.

ADVISORY COMMITTEE MEMBER PLOPPER: Yeah, that's what -- yeah.

CHAIRPERSON KLEINMAN: Earlier in the day I believe it was Richard Bode that said that -- or asked the question: What does it mean when you have a model -- an epidemiological model that shows a result of NO2 and then when you add in co-pollutants the parameter -- the slope stays the same but you lose statistical significance? And I wanted to throw that out to our --

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, I forgot, I wanted to mention that too.

We see that a lot. And basically I tend to ignore the fact that the confidence interval widens when

you have highly correlated pollutants. So if you -- you know, if you talk to some statisticians, that's what they'll tell you: You know, you really just need to look at the point estimate and how the point estimate changes for the two pollutants. If the point estimate doesn't change, right, that's confounding or not confounding, whether it does or does not change.

So I think in some of these cases, while they became, when you put NO2 with PM, not statistically significant, the confidence interval crosses zero, the point estimate didn't change. So that really mean there's no confounding by PM.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: It usually means it's more classic colinearity.

ADVISORY COMMITTEE MEMBER DELFINO: Yes.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Because colinearity should not affect the beta estimate, but will make the confidence interval change depending upon the co-variation structures. So, yeah, I think what you're saying is right.

I mean this two pollutant model thing is an interesting thing. I think it can be used in one direction but not in both. For example, I think if you have, let's say, a PM effect and you throw in other

pollutants in the model and you see the PM effect hold, that's pretty good evidence that there's really something going on.

On the other hand, if you throw in highly correlated covariants, whether it be pollutants or weather or whatever, and the PM effect goes away, I don't think that's an argument for no PM effect.

ADVISORY COMMITTEE MEMBER DELFINO: Right.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: That's an argument for colinearity and an instability in the estimate.

ADVISORY COMMITTEE MEMBER DELFINO: Instability in the estimate, yeah.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So --

CHAIRPERSON KLEINMAN: But I think that's the key word, the "instability". If the point estimate stays the same, then I wouldn't classify the model as unstable. It's only when you have this colinearity, and all of the beta, it sort of loads into one factor, to the detriment of the other. And it sort of depends on which one has the slightly higher correlation with whatever endpoint it is you're trying to correlate with as to which enters into the --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: It depends on now -- it also depends on the relative measurement error of the two pollutants. And it also depends on a fairly complex way among the -- actually among the correlation between the pollutants, not even the simple correlation. But you can have -- anyway, it gets pretty complex.

So it depends on the correlation between the terms and of the terms -- each of pollutants with the dependent variable and the associated measurement errors of each of those things. And that can determine how these ultimate beta coefficients shake out.

So I don't think it's appropriate to say, as even I've said, that when you have a two-pollutant model and one of the pollutants is stronger than the other, that means it's that pollutant, because it's not that simple.

ADVISORY COMMITTEE MEMBER SHEPPARD: Just a general comment on how this chapter's put together, Chapter 7. It's a lot harder for me to extract what the overall effects -- or results were from epidemiologic studies from this chapter than it was, say, from Chapter 6 on the effects of exposure chambers. Maybe it's because I don't know the field as well. But I don't -- I think it was -- you know, when I heard your presentation this morning, there were slides that summarized five or six different studies that show associations between NO2 and

respiratory disease and a series of studies that suggest association with emergency room visits and increased severity of asthma and NO2 exposure. And in the document, it's much harder to see those things. They somehow -- maybe it's a function of how this chapter's organized, but the -- for example, in trying to track from Chapter 6 to Chapter 7 to see is there a coherent body of data that links the exposure chamber studies on asthma to epidemiologic studies of asthma, it's hard to extract the -- in fact, I got it much better from your PowerPoint slides than from the chapter.

I don't know if other people have had a similar impression.

But that's a sort of -- unfortunately a fairly major global sort of comment.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: I agree with what you're saying. And I think it reflects the fact that we finished this draft, whatever -- three or six months ago and went through our reviews. And then as one sits back a little bit, lets it sit and then really tries to go through all the evidence of all the different types of studies, sometimes you glean patterns that you don't necessarily see when you're cranking for a lot of hours on one chapter, you know.

So really when I -- really when Janice and I and

Melanie and Shelly started sitting down and really going through all the evidence, including the tox evidence, and were really starting to get a picture of the real coherence, which I didn't really think was there a year ago. I was starting to see it six months ago, and last month I was seeing it even more clearly.

So I think the slides I presented today are maybe our clearest integrated thought on it. And I think it's fair to say that we're going to be rewriting the "Recommendations" chapter and part of the "Epi" chapter to highlight more of what we ultimately came to realize.

ADVISORY COMMITTEE MEMBER SHEPPARD: Yeah, I think it's important for NO2, because as -- you know, we were talking about earlier this morning that the data aren't as -- each individual study isn't as clear. So, you know, you can find studies that contradict one another. But it's really the cohesion of data from multiple sources.

So if these chapters are organized in a more parallel fashion so that you can see those connections a little bit better, that would be very helpful I think.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: (Nods head.)

ADVISORY COMMITTEE MEMBER SHEPPARD: The other thing -- the other point I'd like to underscore is one

that I think Charlie was getting at, which is it maybe doesn't come across strongly enough, that the -- there's a signal to the noise problem with the way most of the epidemiologic studies have been done because they depend on the monitoring systems that are in place that make measurements far away from where the people are who are actually potentially being exposed. So that, you know, in this case I think you can make a pretty strong argument that anything that is identified is probably an underestimate because of the -- you know, the differences that Ralph is talking about between individual exposure assessments and, you know, central site exposure assessments. So it would be good if somehow that came across a little bit more clearly in the chapter.

CHAIRPERSON KLEINMAN: Okay. Are there other comments on Chapter 7?

If not, we'll move on to toxicology.

And was it David wanted to --

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Yeah. Bart, you wanted Daryn Dodge to do an outline on toxicology?

(Thereupon an overhead presentation was Presented as follows.)

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah.

So I think Daryn Dodge is just going to give about ten-minute overview of some of the toxicologic findings as a lead-in to the discussion here.

DR. DODGE: Okay. I'll just jump right in here and say that the emphasis was on studies that had been performed since 1992. The first go-around for the NO2 standard occurred in that year. But there were some important studies included that were prior to this, and also some studies that might have been missed in the first go-around.

And we were looking at concentrations of one part per million, the studies that looked at those levels and below. This knocked out a number of studies because some of these -- many of these animal studies were looking at concentrations of 10 or 20 parts per million. And we wanted concentrate on those studies that were more relevant to what humans might be exposed to.

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DR. DODGE: The way the information here is organized, we're going to look at dosimetry models in animals and make a few comparisons to humans: Adverse effects, acute and short-term studies. And these are broken down into healthy adult animals, young animals in which their lungs are still developing, and sensitive animal models, and enhancement of allergic reactions.

And then, finally, look at some adverse effects in chronic studies. There were really only one chronic study that had come out in the last 10 or 15 years, and that was in rats.

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DR. DODGE: For dosimetry models I just really wanted to say that, you know, based on the knowledge of anatomy and morphology, you can make some estimates in the amount of NO2 absorbed at lung target sites in the animals. And from that you can estimate where you're going to see the damage based on whatever concentration you're working with of NO2.

And these models in animals reflected what was seen in the exposure studies in animals. So that sort of corroborated that the models were correct.

And the primary site of the lung damage based on these models and in the exposure models as well was the bronchiolar-alveolar duct region. This is a transition from the conducting airway to the gas exchange airways. And it's also known as the centriacinar region, or at least that's how I knew it back in the early nineties.

And comparisons were made by Miller and Associates in 1982 looking at several animal models as well as a model for humans. And the site of damage is similar for humans as well as animals. But there were

some slight differences in their models.

Highest or maximal tissue dose -- that's the actual concentration that reaches the tissue -- in the terminal respiratory bronchial in humans -- that's where you see the most damage. In rodents it's actually slightly distal to this in the alveolar duct, but still in the same general area of the centriacinar region.

Another difference they see with their dosimetry models is that in humans the NO2 tissue dose is about two to four times greater in humans when compared to rodents.

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DR. DODGE: Now, among the studies that looked at acute and short-term exposures in adult animals, in general, they weren't seeing any lung edema or any sorts of morphological histopathological changes at concentrations of one part per million or less. Generally the effect was seen at two to five parts per million. And this was in rats, mice -- and GP stands for guinea pigs there.

The changes that they were looking at were influxes of inflammatory cells into the lung, as well as increases in protein in lavage fluid.

Well, having said that, there are some subtle changes that are seen at lower concentrations. You see a decrease in arachidonate metabolites in lavage fluid.

These metabolites are such things as prostaglandin, F2 alpha in E2 thromboxane B2. And these effects are seen largely in exposures of four to eight parts per million, but also in some intermittent short-term exposures, the five to ten days.

Now, these metabolites are important to the lung because they help regulate how the lung responds to infection, inflammation. If you change these levels, you could have an inappropriate response with the -- to inflammation or infection in the lung.

You also see a decrease -- an increase in epithelial cell labeling. This is in the bronchiolar or distal airways. It's an indicator of cell turnover and indicator of cell injury as well. And this occurred at .8 part per million, 24 hour exposure.

In alveolar macrophages, ex vivo -- this is where the animal's exposed. And then the macrophages are flushed out and tested. You see a decrease in irrelevant arachidonate metabolite release at .5 parts per million and a decrease in the release of superoxide. Now, superoxide ion is important because it has a direct cytotoxic effect on invading cells or infectious agents.

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DR. DODGE: There were a number of in vitro studies as well.

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DR. DODGE: At .5 to 1 part per million you see an increase in aldehyde generation. And this is in epithelial monolayers as well as macrophages. Increase in aldehyde generation is due to the interaction of NO2 with polyunsaturated fatty acids in cellular membranes. And that's what generates the various types of aldehydes. You also see an increase in membrane sodium potassium pump activity and an increase in ion transports in epithelial monolayers at 1 ppm, indicating there's a disruption in salt balance across the cell membrane.

Now, in macrophages only in vitro studies show a decrease in superoxide production, which is the same as the ex vivo results in the macrophasges. However, you see an increase in arachidonic metabolites. And this is with ionic bore stimulation only at one parts per million. Now, this didn't really reflect what was going on ex vivo or in the intact animal. So you really can't make comparisons all the time with in vitro studies with the intact animal.

At .2 part per million there was a study that looked at bovine macrophages and saw an increase in the nitric oxide production. Nitric oxide has a cytotoxic as well as a regulatory effect in the lung for infectious and inflammatory-type reactions.

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DR. DODGE: Probably the most interesting results is in young animals in which their lungs have not fully developed. There was a series of studies in young ferrets. The ferrets were used because their lung development was similar to -- more similar to humans than rodents. In these ferrets, they were exposed beginning at six weeks of age to .5 ppm four hours total per day for 15 weeks. And you saw a number of effects indicative of inflammation, including increased inflammatory necrotic cells in the lung, increased septal wall thickness in parenchyma cellularity, decrease in alveolar diameter in cross-section area and an increase in the lung volume to body weight ratio.

And there's also a series of studies in young mice by Dr. Sherwin's work here. And what he looked at was exposures .25 to .3 part per million. And you saw some changes here in the structure of the lung, particularly in the parenchyma here where we have an increase in elastin content. And you see an increase in the oxident tolerant type 2 cells.

Now, what was interesting here is that these changes were noted 32 weeks post-exposure. So there appears to be a persistent or at least -- or a possible permanent change to the lung structure here.

Now, you compare this to the chronic study I'm going to show in a little bit where rats were exposed to an average greater than .5 ppm for 78 weeks, they didn't see these changes in lung structure. But the animals -- or the rats were exposed when they were adults. Their lungs had already fully developed.

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DR. DODGE: There's one sensitive animal model that I found. And this looked at an obese rat model, where it's very sensitive to cardiovascular disease. And what they found with exposure to .16 parts per million for 24 weeks -- that was continuous exposure, by the way, for 24 weeks -- you see an increase in atherogenic indicators. And this includes a decrease in high density lipoprotein, or HDL, the good lipoprotein, a decrease in the HDL to total cholesterol, an increase in triglycerides.

And they even saw a decrease in the HDL in the genetically related normal rat stream under the same exposure protocol. The author said this was important because in human studies -- or there's an association between oxident exposure and indicators for atherogenic disease in sensitive humans, in particular those with diabetes and those with severe types of atherogenic disease.

Now, at higher exposures they saw actually a

decrease in these indicators, at .8 and 4 parts per million. So no dose response was observed at least in the direction they would like to have seen. But they say that the exposure here exhibited a u-shaped dose response. In other words, they saw effects at low exposure. But as the exposure concentration increased, other factors came into play and you don't see these effects.

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DR. DODGE: Now, there was a series of studies that looked at the enhancement by NO2 on models of allergic airway disease in animals. And we were looking at concentrations here greater than 1 ppm.

And in this these models, many of them were performed the same way in general, in which the -- there was an antigen used to sensitize the animal. And then sometime later -- some days later you'd give a challenge dose of that antigen followed immediately by NO2 exposure.

Now, the timing of the nitrogen dioxide exposure could vary. Sometimes they expose the animals during the entire priming and challenge phase.

But what was seen again in general was that they really didn't get an enhancement of allergic airway disease or any indicators thereof at concentrations less than 5 parts per million.

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DR. DODGE: What was seen at about 5 ppm and higher was seen down here. This is a study by Gilmore and Associates, in which they exposed the animals to house dust mite antigen to sensitize it and then gave a challenge dose. The animals were exposed to NO2 for three hours, both immediately after sensitization and after challenge. And you had these increases in these indicators of allergic airway disease include increase IGG, IGE, IGA in the bronchial or alveolar lavage fluid.

Now, in these studies here there was no particular -- or specific antigen involved. They just simply exposed the animals to 1 ppm for 12 weeks. And this was again a continuous dose -- or a continuous exposure. And you saw an increase in airway hyper-responsiveness to histamine mean challenge. And at 4 ppm in guinea pigs you'd see an increase in IGE-mediated histamine release. Well, what was interesting, they had rats exposed to the same exposure scenario and they didn't get this increase in IGG-mediated histamine release.

--o0o--

DR. DODGE: Now, in the one chronic exposure study that's out there, it was in adult animals again. I mentioned this already briefly. The exposure scenario was a background concentration of .5 ppm with daily spikes up to 1.5 ppm for 78 weeks. This is to reflect something

closer to human exposure to ambient air.

And they looked -- they were pretty comprehensive and looked at a number of endpoints. But what they -- what was considered significant was down here. And it was actually transient effects. At 70 weeks only you see a decrease in the delta-forced expiratory flow at 25 percent vital capacity, which reflects an increase in the resistance of normal breathing. However, 17 weeks following exposure the animals were normal with respect to this endpoint. They also saw a decrease in natural killer cell activity, but this was at 3 weeks only. It wasn't seen at 78 weeks.

--o0o--

DR. DODGE: Well, in summary, the acute lung injury effects begin at around .5 to .8, the alveolar macro function changes occur at .5 ppm or greater. The cell membrane peroxidation products -- this is the in vitro studies that saw an increase in aldehyde generation -- that's at .5 ppm.

The lung development changes were seen at .25 ppm, and markers for cardiovascular disease seen at .16, and the allergic asthma enhancement at 5 ppm.

Now, probably what I'd -- what would be nice to see is, in terms of this allergic asthma enhancement, exposures in young animals. All of the results that I

mentioned occurred in adult animals. And only one study I think looked at allergic asthma enhancement in a developing animal. But yet they didn't see any effects.

And that's it.

CHAIRPERSON KLEINMAN: Sure.

ADVISORY COMMITTEE MEMBER SHERWIN: In the technical document you point to a few other references, Richters, Kuraitis, on immune phenomenon. Should that not be in here as well?

DR. DODGE: I think I included some of that information in the TSD.

ADVISORY COMMITTEE MEMBER SHERWIN: With what?

DR. DODGE: In a technical document.

ADVISORY COMMITTEE MEMBER SHERWIN: Well, it's in the technical document, right. But it's not mentioned here. I was just wondering why this summary doesn't have it. But it is in the technical document. And I just -- but you didn't bring it up here. So I was just wondering why.

DR. DODGE: Yeah, I didn't have enough time to really go in to that.

ADVISORY COMMITTEE MEMBER SHERWIN: Oh, okay.

Another question is, neither in the technical document nor in here or in the staff report are there some other toxological studies, personal ones. One is 0.4 with

protein leakage. In fact, I have about two or three of them where mice, guinea pigs -- I'd have to go back and look. Well, let's see what I have.

DR. DODGE: That information might have been included in the previous NO2 standard in -- reviewed in 1992.

ADVISORY COMMITTEE MEMBER SHERWIN: Well, I think it's -- I consider leakage so important, that I think it weakens yours argument in support here if they're not included in the text of a document. There -- I mean others besides myself have come up with permeability of one the critical things that are -- that's going on.

Another thing is -- which may or may not have been in a prior document, I don't recall -- but we did a study at 0.4 ppm and showed a diminishment of diphosphyl glycerate. And that was I think in guinea pigs exposed to NO2.

What is that? Well, hemoglobin and diphosphyl glycerate are interwoven in terms of oxygen transport. So a perturbation of that particular comple -- I mean the diphosphyl glycerate could have significance. Now, at 0.4 I just think it's something that warrants mention as much as some of the others which are also, you know, unconfirmed or still pretty iffy.

But what it does point to is that there are some

key areas that haven't been looked into. If I'm worrying about oxygen transport, which is the real thing the lung is supposed to do, and somebody says, "You know, red blood cells play a role in oxygen transport too," say, "Well, how about diphosphyl glycerate, does that" -- anything perturb the hemoglobin? And the answer is, well, there is that study.

And then a final thing I should mention is that the macrophage is, in my mind, the central figure in this whole toxicologic area. I don't think it's been given enough stress. There are a number of papers that have come out, the Kelly paper, for example, on oxidant -- anti-oxidant. But the real part of this is the damage that oxidants do to macrophage. They seam to be a central figure. Let me give you two examples.

Central to silicosis is macrophage. All silicosis, silica granules begin with damage to the macrophage, release of cytokines, chemokines, all those gene factors.

Exactly the same thing is true of asbestosis. When you get down to say what's the core phenomenon, it's the macrophage, right at the core. Everything stems from that.

So the macrophage plays an important role in cleanup, plays an important role in lymphocyte

interactions. But the most important thing, it's a dangerous cell. When you hurt a macrophage, you release some terrible enzymes and proteases. You name the noxious agents that come out of macrophages.

So somehow I think a little more emphasis in the toxicology on the need for more work on the macrophage playing a central role and especially in terms of NO2 studies that may have shown macrophage damage. Remember, the macrophage is a key thing in lung disease. We have one early form of interstitial fibrosis, a little bit controversial whether it goes on to fibrosis. But I think it does. It's a thing called desquamate of interstitial pneumonitis. And that's the macrophage pouring out into alveolar.

Well, all this is, you know, maybe more than you wanted to hear. But, again, if the macrophage I think is a central player, and we don't have much data on it, it somehow should be brought out as one of the needs to really support -- well, a need to come up to support this kind of data. Or the other side of it. We have much more support coming to us if we follow up on some of these important things.

The protein leakage I think is not being emphasized properly. Well, I won't properly. It could be emphasized more. And the diphosphyl glycerate I think is

worth mentioning.

The lymphocyte study have been mentioned. But, again, I think it's -- for example, you have an AIDS population. What's the big thing about an AIDS population? A shift in lymphocytes. Foresee a shift. They get depleted. There's one population very susceptible. What is the story on AIDS people in an area of high NO2? I don't know anything about that really. I think I looked it up once, but I didn't find much. But that certainly -- now, that's -- you can say that's a very select population. But, boy, it's certainly an important select population.

So those are things that say turn it around. You got some AIDS patients and they come up to you and they call Charlie Plopper and -- just when -- haunt him on something like this and say, "I have a relative who has AIDS. Is it bad to live in Los Angeles with high NO2 or ozone or whatever?"

On that feeling alone, I would say, you know, I don't feel comfortable with point -- certainly don't feel comfortable with .25 parts per million. I don't feel comfortable with .18 when it comes to an AIDS group. How much does it facilitate, promote, exacerbate AIDS if it isn't -- obviously not a prime cause?

So these are the kinds of things I'm trying to

bring in to say much of the problem has yet to be defined, much of the technology has to be beaten up. And Dr. Platzker's bringing up cystic fibrosis points out how important prioritization of susceptible groups becomes in understanding where we stand on NO2.

CHAIRPERSON KLEINMAN: Okay. So I'd like to turn it over to Dr. Plopper. Comments.

ADVISORY COMMITTEE MEMBER PLOPPER: Sure. I'd like to say, first of all, I think you did an admirable job with the literature there. It concerned me at first, and then I realized that this is not the ozone literature; this is the NO2 literature, and most of the stuff isn't there, so you can't make a lot of broad judgments because there's no data.

And that's -- but I would say that I think it would been stronger -- it would be a stronger presentation to not have an appendix but just to put this material in the front. And I think that this summary that you gave us would definitely help, because I think one of the confounding issues here is the fact that there's not a lot of information for a large number of areas that are of concern for health because there's just -- nobody's done the experiments and I doubt that probably anybody will because I don't think anybody's going to give anybody any money to do it. And I think that's reality of the

situation.

So I think that you've done a good job with what's there. But I think that the effectiveness would be -- I guess my concern when I read this is that it gives the impression that there's not a lot of toxicology data that says that there's a big problem here. And I think that Russ has already outlined some of these.

I will say one other thing that struck me as I went through this was that when I think about the ozone literature, I don't -- I'm trying to think of studies where actually somebody did an exposure at a current standard and found something. And there's a study that goes at the standard and finds major changes in developmental problems, and the short Chapter 8 at the beginning doesn't even mention that study anywhere. And I think that's a -- I think that this would be much stronger if it were -- if you didn't have an appendix. Because I read the appendix by reading a subtitle in the front and then reading everything in the appendix and then going back again. And I think it dilutes it tremendously. I actually feel that it downplays the fact that there are changes that outplays Russ's study in terms of what the problems are, because I don't -- I'm still not -- if we get an effect of .12 with ozone, that's a major deal. And I don't see that I've seen a study that's shown any effect

at the standard, even the old standard, much less the new one. And I think that -- I mean I'm wondering if .18 is low enough, because I mean -- you know, I mean no one in their right mind would do a study if -- an exposure study in animals if they didn't expect to find something. So nobody would go for the standard because they don't expect to find anything. But there's already somebody who's found something.

And so I don't know if I'm being very comprehensive about it. But I think that the tables that you have in this presentation would be helpful. I think that it -- the other thing, because the literature is so minimal compared to what's available, the voluminous documents for ozone, for instance, that it would be very useful to have a statement at the beginning as to what was found before, because some of those studies are what there is. So rather than ignore them in this or assume that somebody will look at them, I think that they need to be summarized. Because Russ already brought up a couple that I would agree are very critical and they're not in here. So were they in the other one? I assume they were.

So it would be helpful to know what was decided before and how we deal with the fact that what was decided to be a safe standard before when used in an experimental situation produced some very startling and possibly

life-long results.

And I had some other minor things. But I think that's the big concern that I have, is that I think it needs to be reorganized. Because in the staff report and in the front of this document it mentions this young animal study. And it's discussed in the appendix, but it's not actually discussed in the front part. I mean I think that's the major new finding from before.

So possibly it would help to have some sort of a summary of what was found before and how that informed the last decision about a standard, then how you reevaluate that when someone actually does an experiment at the standard and finds something. That's pretty -- that's relatively unusual I think.

The other thing I thought was at the conclusions that were in the appendix on A-68 and 69 do a nice job of summarizing what the issues are at this point, and they should be up in the front somewhere and not stuck in the appendix.

So I think that was probably my main concerns.

DR. DODGE: Okay. So we'll try and move that up front then. And I also include some of the studies that Dr. Sherwin mentioned concerning macrophages and leaky lungs.

ADVISORY COMMITTEE MEMBER PLOPPER: But I think

in this case it also needs -- because the data is so small, that the number of experiments is so minor, that it needs something that discusses what was there before. Because you can't by reading this -- my immediate reactions were, "Why the heck did somebody pick a standard for before that was shown to have substantial effects?" So there needs to be some history in here at least for this part because there's not a lot of data to work with.

And I think it would also be helpful to identify things -- and possibly that means going back to something like the ozone documents, since there is so much, is just to look at all the categories of studies that were discussed and point out where those categories of studies can't be discussed in this document because nobody's done experiments there.

I mean it doesn't hurt to identify things that are not done here because it can give the wrong impression about how something is decided.

ADVISORY COMMITTEE MEMBER FANUCCHI: I'd like to reiterate some of the stuff that Dr. Plopper said, that I think it was an admirable job to pull this all together. And I do agree that since there isn't that much data, I think the appendix could be Chapter 8, because I actually spent most of my time reading the appendix first.

Some of the ways to reorganize this I think would

make the animal studies more helpful, because to me right now it's not very transparent how the animal models can help set the standard or can be used to help set the standard. One of the reasons for this review was because of the susceptibility of infants and children. And I think it would be very important to talk about why lung development is an issue for these standards and what critical windows there might be that we have to be concerned about. And, again, like Charlie just mentioned, that if you lay it out and you show our gaps in knowledge, I think that that would maybe help push forward some research that needs to be done and to give us reasons for putting in safety margins, because we don't know what's going on in all the lung development.

I think on that same thought, because a lot of the allergic responses haven't been done in young animals, you have the same sorts of issues that need to be delineated for the development of the immune system. And I think along with that is maybe a little discussion about what would be an appropriate animal model for these things. Partly because I know, as was stated in the appendix, that most immunologists are going to pick a mouse. Anyone who does immunology in a human or a primate will say that a mouse has nothing -- does not develop immunologically like a human. So trying to force that

sort of study on to a rodent is not going to give you the kind of information that you need.

So I think it would help to have some of the issues laid out and then the studies will fall into place. And if they don't fall into place, then we know we have a huge gap in knowledge.

One of the other things, I think that the animal studies may not be showing effects all the time is because the morphological lesion is a very focal. And most of these studies are based on bronchial alveolar lavage, which any effect in the centriacinar region will be diluted by the vast number of cells that come out of the parenchyma gas exchange region. Also one of the them that's glaring is that they did whole lung homgenates and looked at anti-oxidant levels.

So if there were issues in those focal regions, you're never going to find them if you grand up a whole lung. So I think those caveats need to be addressed in there, because we may be underestimating how much help the animal studies can be or how they were done.

DR. DODGE: Okay.

ADVISORY COMMITTEE MEMBER FANUCCHI: Yeah, I think -- yeah, the biggest thing would be to put upfront some of the issues that we're dealing with and a clear summary. And you did a nice job on the presentation. So

I think to focus on having that right upfront would help the reader understand.

Also, I don't know how this works. But it wasn't clear to me how the dosimetry was being used to help with the standard. There was a discussion about dosimetry and tissue dose between different species. But I didn't really get a feeling for how that dose was being extrapolated back to humans. I don't know if it's been done. I don't know if it's part of the process of setting the standard. But it would seem to be helpful.

DR. DODGE: At least with regard to NO2 there really isn't that much there. The information I could find where they attempted to make comparisons to humans was 1982, the Miller study. You know, there's a lot more for ozone of course. There just isn't that much for NO2.

ADVISORY COMMITTEE MEMBER FANUCCHI: Yeah.

CHAIRPERSON KLEINMAN: However, I think in your presentation you mentioned that the delivery to the rat is one-third or one-fourth the dose that a human would get for the same exposure. So if those numbers make sense, then, you know, the appropriate level for an animal exposure would be something like three to four times the exposure that you would use in humans. So it would not be, you know, out of the pale to do a rat exposure at 1 ppm, which might be relevant to human exposures at .25.

DR. DODGE: Yeah, that one was of the factors in kind of choosing 1 ppm as a --

CHAIRPERSON KLEINMAN: Yeah, but that's not in that section on dosimetry in the document. So it would be good to at least address it.

Now, that's very speculative. And a lot more work probably needs to be done to clean up and to really refine those dosimetry estimates. But I think that's one way to start putting that data in context.

CHAIRPERSON KLEINMAN: I'm sorry. I didn't mean to interrupt you.

ADVISORY COMMITTEE MEMBER FANUCCHI: No, no. And I can't emphasize enough that -- you know, with ozone we never really came up with a feeling that there was a threshold for an ozone exposure. And there really is no discussion about threshold for NO2, you know, is there a threshold, because I don't think we understand the mechanism of NO2 injury enough to make those decisions. But I think a discussion of whether or not there's possibly a threshold, because there is -- you know, there's only that one newborn mouse study here, but it was pretty striking. And I think that should be emphasized more because -- I mean if you mess up your lung that early, you're going to be -- you know, chances of you having long-term consequences are huge.

So thresholding and then more emphasis on the neonates and maybe some emphasis that this could be a research area, that needs to be looked into.

ADVISORY COMMITTEE MEMBER CHESTNUT: I just have one little thing on this kind of presentation here. I think it would be helpful to add something about the length of exposures. It seems like -- I don't know the details, but a lot of these were longer term exposures. So it's not the peak of .25, you know, on occasion. It's they're at that level for several weeks at a time.

DR. DODGE: Yeah, that's correct. I didn't show that information on this particular wrap-up slide.

ADVISORY COMMITTEE MEMBER CHESTNUT: Just help us understand how these might relate to the ambient levels we're talking about.

ADVISORY COMMITTEE MEMBER FANUCCHI: Actually that brings up another question.

When you said continuous exposure, was that 24 hours a day for three weeks or something or --

DR. DODGE: Yes.

ADVISORY COMMITTEE MEMBER FANUCCHI: So that's a completely different exposure than any person would be getting. And based on some of the work that's been done in rats and monkeys on ozone, it's an exposure and then rest period and exposure and the rest period that's really

dangerous. So being exposed continuously will give you a completely different response than even a daily exposure; is that correct?

ADVISORY COMMITTEE MEMBER PLOPPER: Well, I think that actually brought up a good point -- I had it in my notes and I forgot to say it -- that it would be really helpful to have that explained what the exposure parameters are. Because actually what that's the result of is that that's a tolerant mouse that actually had their lungs destroyed, which is pretty -- that would concern me that lowering the standard to .18 is not going to do anybody any good. I mean I just -- I mean I've just been dealing with ozone for a long time now. And ever even getting close to the standard, I just always assume that's going to be a write-off because we're not going to find anything. And right now we're sitting here arguing about exposure protocols that used the standard. I mean that just -- for me, the more we sit and talk about this, the more I get concerned about it, because it just isn't in my world view. I've only done -- ever done one study that close to the standard, and it barely found something. And you got big changes here.

ADVISORY COMMITTEE MEMBER SHERWIN: Michael, may I make just add one comment?

CHAIRPERSON KLEINMAN: Sure.

ADVISORY COMMITTEE MEMBER SHERWIN: On the markers -- I think some of this session should be sort of encouragement and new ideas that might be useful to young investigators. And under the markers it would be nice to have markers for thrombosis, blood clotting, because we know that there's an influence of NO2 on micro eboli and micro thrombosis. We know there's lung leakage. We know incidentally that pulmonary emboli in women are very common. It's not that common in men, but for some reason there's a lot more phlebothrombosis in women, pregnancy and whatever. I find signs in autopsies of pulmonary emboli in almost all women, you know, past the child-bearing age. So there's been signs of emboli.

Now, who runs into trouble? The women who get an embolus and lung leakage at the same time, like in conjestive heart failure. They get pulmonary infarcts. So markers -- you could have some very sensitive changes -- if I saw markers from .18 or .16 in somebody that's just shown here, I would start thinking about a lower level than .18.

So I would like to see in the priority list of things we're putting down of the markers, aside from all the others we mentioned. Markers were plenty. And there are myriads of them, very sensitive ones. That should be part of the studies. I haven't seen anything like that.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: Can I just make one comment?

CHAIRPERSON KLEINMAN: Sure.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: This is Melanie Marty.

Just in listening to the discussion about the .18 standard, and comparing it to the lung developmental changes, I just want to note that that lung developmental changes were from a sort of chronic/subchronic exposure paradigm. And so it's almost more appropriate to compare that to the proposed long annualized average standard of 30 parts per billion. You know, the truth is it's kind of really somewhere in between a short-term and a chronic exposure.

So just to get that -- to get you thinking looking at that.

ADVISORY COMMITTEE MEMBER SHEPPARD: I just had I guess a question, Russ, maybe for you about your 1985 study. So if I remember correctly, you did -- I don't recall measurements of there being differences in alveolar size or in -- was there some --

ADVISORY COMMITTEE MEMBER SHERWIN: Well, some -- yeah, there was a couple studies showing enlargement of alveoli.

ADVISORY COMMITTEE MEMBER SHEPPARD: Because the

measurements that I remember -- the ones alluded to here are --

ADVISORY COMMITTEE MEMBER SHERWIN: I didn't do such measurements, no, because I didn't --

ADVISORY COMMITTEE MEMBER SHEPPARD: And at these concentrations there were changes -- there were morphologic effects that suggested injury and repair, right?

ADVISORY COMMITTEE MEMBER SHERWIN: Well, the most important thing I thought -- it was a personal work that interested me most -- was damage by NO2 was at, it was pointed out, at the centriacinar area. And the cardinal lesion is damage to the epithelial -- the thelia and epithelial line in a type 1 cell. The type 2 cell is a replacement cell. So any time -- I see type 2 cell hydroplasia as a common finding in lung disease.

So it is reproduced at .3 ppm in mice, and we did that in a numbers --

ADVISORY COMMITTEE MEMBER SHEPPARD: I guess maybe I was reacting, Charlie, to your suggestion that the lungs are being destroyed by the --

ADVISORY COMMITTEE MEMBER PLOPPER: Well, being disrupted. I'm not -- I'm sorry.

ADVISORY COMMITTEE MEMBER SHEPPARD: Sorry. I mean I think --

ADVISORY COMMITTEE MEMBER PLOPPER: But there's a significant change --

ADVISORY COMMITTEE MEMBER SHEPPARD: There was evidence that there's morphologic evidence of injury and repair in the periphery, which is of concern. Probably not it means that they were being destroyed.

ADVISORY COMMITTEE MEMBER PLOPPER: No.

ADVISORY COMMITTEE MEMBER SHEPPARD: So was there a reason for doing this -- for setting up this chapter with a short chapter and then a large appendix and all of the rest of them in a different way?

DR. DODGE: I think it's --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: I can answer that.

It was a pretty -- it was a silly bureaucratic reason, to be honest with you. That everybody felt, well, the emphasis for the standards is on the human studies. So the toxicology studies is, quote, supported. So let's put it in an appendix. And we argued back and forth whether it should be a chapter or whether it should be an appendix. And clearly it should have been a chapter.

(Laughter.)

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: We will fix that.

DR. DODGE: It also mirrors what was done for the

ozone standard as well.

ADVISORY COMMITTEE MEMBER SHEPPARD: Again, I think the way it -- one of the ways that it really -- of having all the data really helps is with this issue of coherence. So the most convincing argument that one could make and I feel that's so complicated is that there's consistency among multiple different lines of investigation. So it seems like certainly for effects on airway hyper-responsiveness and allergan responsiveness and for lung development you have either two or three of the different lines of investigation that support the likelihood that those -- that such effects might occur. So the toxicology really -- you know, having it fleshed out really does help.

ADVISORY COMMITTEE MEMBER PLATZKER: Is part of the activity here to speculate on what has not been done and to postulate how to do a good experiment in the future?

CHAIRPERSON KLEINMAN: I think that could be among the recommendations that we provide to them, you know, recommendations for future research and experimental designs.

ADVISORY COMMITTEE MEMBER PLATZKER: Because in pediatrics now, we -- there isn't any blind period in which you cannot do pulmonary function. Infant pulmonary

function now is very elegant. You can get data as good as adult data from infants, from birth to about three years of age. In our group we've done studies looking at routine spirometry in children from three to six. And in two-thirds of the cases even at three years of age you can get good data.

So, you know, it would seem to me that depending -- and the individual parameter that you want to look at is different in various age groups. For example, at birth V-Max FRC is an important pulmonary function parameter. In older infants V-Max 50 percent is very important if you're looking at medium and small airways. And in older children we look at V-Max 60 to look at small airway involvement.

So that it would be important if somebody's going to do research or fund research, that a group like this speculate through the life cycle what studies need to be done and what you should look at in the future so that the research dollar can be maximized in terms of the term.

CHAIRPERSON KLEINMAN: Are there any more comments relating to the mechanisms of toxicity or other issues that, you know, relate to the toxicology chapter?

No. Okay.

So Chapter 9.

ADVISORY COMMITTEE MEMBER SHERWIN: Michael, let

me ask --

CHAIRPERSON KLEINMAN: Sure.

ADVISORY COMMITTEE MEMBER SHERWIN: -- a peripheral question.

But in the old days I remember -- and correct me if I'm wrong -- a 0.15, 24-hour NO2 standard. Is that a real recollection or did I --

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Say that again.

ADVISORY COMMITTEE MEMBER SHERWIN: A 0.15 ppm, 24-hour NO2 standard. Wasn't there a standard of that sort?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: I don't think so.

ADVISORY COMMITTEE MEMBER SHERWIN: Well, it raises -- the question I'm leading up to is -- we have two extremes. One is a one-hour average, and then we have an annual. The dogma says -- or the general principle that's accepted is that peak values are much more important than dosage. But if I had a level of .15 NO2 all week long -- and I've seen this happen. I remember looking at a winter one time when what happened I guess in the future unless the cars -- well, I don't know. Maybe -- got thrown right now. But, anyway, if I saw that for three weeks in a row, I wouldn't exceed the standard. A .15 would not beat your

.18.

But would that be a service for the protection of the public health to have 21 days of that kind of level and say it's okay? I'm almost sure that there was such a -- there was such a -- do you remember that at all, Michael.

CHAIRPERSON KLEINMAN: No.

ADVISORY COMMITTEE MEMBER SHEPPARD: There's a 24-hour sulfur dioxide.

ADVISORY COMMITTEE MEMBER SHERWIN: What?

ADVISORY COMMITTEE MEMBER SHEPPARD: There's a 24-hour sulfur dioxide.

ADVISORY COMMITTEE MEMBER SHERWIN: No, no. No, no. This is definitely on -- this is my business of NO2, because I remember looking at the records and find -- I was so surprised to find there was a level that fell below the standard for that.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: I think it might have been a -- because actually the .25 actually has been pretty well set for about -- since about 1966 is the NO2 standard for one hour. But it might have been like an emergency level or a --

ADVISORY COMMITTEE MEMBER SHERWIN: Well, the principle is all I'm interested in. And, that is, in your guidance should you be concerned with long-term durations

at that high level -- what would be called substandard levels at prolonged periods, should that be a concern?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, I mean the fact of the matter is you get significant diurnal patterns in NO2, right? So you get really big changes during the day. So, if you had a quarterly average, let's say, of .15, you would likely have some hours within that period that were substantially higher than that, so that it would therefore not be an attainment for the one-hour standard.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: So, Melanie, you just pointed out there was -- I guess in 1959 there was a .15 ppm, it was an oxidant standard, which probably covered NO2 and ozone and all the oxidants at one time, like in '59.

ADVISORY COMMITTEE MEMBER SHERWIN: It was an ozone standard?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: It was an oxidant standard. So it covered --

ADVISORY COMMITTEE MEMBER SHERWIN: Oxidant standard, right.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Yeah. So it covered NO2, ozone, all the oxidants --

ADVISORY COMMITTEE MEMBER SHERWIN: Well, the

principle's the same. It's just a question of -- an annual standard -- to me an annual is almost -- I hardly look at an annual standard. I don't think --

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: And actually that was one hour. So that .15 was a one-hour standard.

ADVISORY COMMITTEE MEMBER SHERWIN: Yeah. But if you average -- imagine the dilution factor over 365 days. That's a phenomenal dilution. It doesn't mean much. So you could have horrendous -- you know, days of high pollution. And I guarantee you, if you diluted out with 365 days, you're not going to be very impressed by it, or you're going to have to have some kind of a factor that says 1/100 of a rise in the annual standard is a health hazard. And that's where I'm -- you know, at what point would you be concerned about a rise in the annual average? What is -- what would be -- what would be considered an alert or an advisory that says we are in trouble last year because we overwent the annual standard -- we rose above it? Is there any such guideline?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Well, the process isn't right now. But I mean right now the NO2 levels are dropping quickly because of all the -- you know, the mandated rules both for fuels -- change in fuels, and -- like we mentioned, the for change

in fuels and also because of the multiple number of controls, a lot to get out the PM concerns as well. So they've dropped NOx levels considerably over the last 20 years.

So we're really being -- right now we're heading downwards quickly. So I think that's why most of the state right now is, you know, in attainment. I think almost all the state's in attainment right now for the one-hour standard.

ADVISORY COMMITTEE MEMBER GREEN: I can maybe add an example of where a one-year exceedance can lead to some regulatory effect. I don't think it's occurred NO2, but I think it does with aerosol. If an air district is exceeding a PM standard, permits for, say, extending freeways or adding lanes on freeways will be held up until there's an implementation plan to remedy that -- even if it's an annual average type exceedance -- remedy that problem and show that it's going to not get worse upon extending a freeway or adding lanes or permitting a new power plant or whatever it might be.

So although you're right, no one's going to announce a second stage NO2 alert based on last year, because what do you do about it? It can have a regulatory impact in industry, transportation, that sort of thing. So that there is sort of -- mechanisms exist to have -- if

a year went to an average 31 ppb in an air district, I think all sorts of attention would immediately come to bear on what's going on there and what have they done wrong and how to do you fixed it?

So it -- although it wouldn't be in the -- on the evening news, you know, air quality for tomorrow sort of thing, I think there are ways for it to -- for an annual average to play a role in identifying a problem and taking preventative action or corrective action.

ADVISORY COMMITTEE MEMBER SHERWIN: I don't recommend dropping them. I just wondered if that kind of a level is realistic. In other words, being in attainment on the basis of an annual average, is it a realistically thing or not?

ADVISORY COMMITTEE MEMBER CHESTNUT: Well, if I could just add, that I think the combination of the hourly standards that addresses the peaks and then the annual average gets you two markers on a distribution that -- that it fluctuates all the time because of the pattern of emissions and then the meteorological conditions that fluctuate, you always have this distribution. The combination of the two probably takes care of a lot in the middle in terms of the 24-hour average, the weekly average exposures. So by adding the annual average to the hourly, you make sure that controls are not just focused on the

very peak days, but you're forcing that whole distribution to stay below a certain level. So I think in a sense it kind of balanced the two pieces.

ADVISORY COMMITTEE MEMBER SHERWIN: Well, my last comment -- it's very difficult for me to evaluate the .03 recommended level. I think it's wise, but I had a very difficult time trying to come up with data that -- even from the standpoint of exceedances, dilution factors. So that's my -- I think we should -- ought to keep it. I think it should be tight. I'm wondering whether there is some kind of an improvement -- for example yes, your annual average and the one hour would be great. But how about a 24 hour or how about an 8 day average; would those be also highly informative and much more so?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: So -- I'm sorry. Are you thinking actually of just placing the question out there, is there a better level for our standard? Not level of concentration, but averaging time.

ADVISORY COMMITTEE MEMBER GREEN: Yeah, time standard.

ADVISORY COMMITTEE MEMBER SHEPPARD: I mean I hear what Russ is asking, maybe is, is there a way to provide modeling data based on what the actual variations in levels are to predict what the impact of an annual

standard would be on, you know, the likelihood that somebody would be exposed for three weeks to an average of, you know, a given concentration. Because that's where the toxicology and human exposure studies and epidemiology would be getting us information about what would happen over shorter periods of time than one year obviously.

So in order to make some sense about rationale for an annual standard, it would seem like you'd need more modeling data that would say what the actual impact would be.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah, I mean we've done some work relating one hour to annual. And you could certainly take any interval within that to see what the ratios are by county. I mean on page A-33, we talk about the fact that the ratio between the -- it's in the staff report.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: The skinny one.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: -- we talk about the fact that the ratio between the 24 hour and the 1 hour is about 4 or 6 to 1. And so you can look a little bit at the consistency between the two standards and in which areas one will be the controlling versus the other. But you could also take any interval less than an annual. Of course you could

look at the whole distribution and get a feeling for the ratio. And as Lauraine mentioned, it will vary of course by county and by year and so on. But you can get a general feeling for what this means in terms of monthly averages or whatever.

ADVISORY COMMITTEE MEMBER SHEPPARD: Yeah, because that's something that maybe should come across a little bit in the body of the technical document, that sort of what basis -- so if you have information about three weeks of exposure to an average -- to a concentration of .25 parts per million affects lung development in animals, you know, knowing that with the expected variation in NO2 concentrations over the day, that the one-hour and annual standard would make it very unlikely that people would be exposed to, you know, any average less than, you know -- or above .05, say -- I'm just making all this up of course. But, you know, that sort of information would really help to make a strong argument for the rationale for the standards. And so -- in this document too.

ADVISORY COMMITTEE MEMBER FANUCCHI: In the small one.

ADVISORY COMMITTEE MEMBER SHEPPARD: Maybe I just didn't read the short one carefully enough.

(Laughter.)

ADVISORY COMMITTEE MEMBER SHEPPARD: Do you have a -- the people who wrote the documents have a sense about the relative importance of the one-your standard compared to the annual standard for protecting against the effects that you're outlying that you want to protect against?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, there's -- I mean there's two answers. I mean one is we've certainly outlined the differential effects that are seen in the different types of studies. You know, clearly you don't see asthma hospitalizations and mortality in the clinical studies, thankfully. So we can only say based on the science that we've seen what it protects against.

But we also have some things in there, some discussion that it could be that some of the epi studies are due to one-hour averages. And it could be you could see worse clinical outcomes with longer term exposures. So certainly there's going to be some overlap between those.

And that's what goes to our margin of safety in some of these. I mean the fact that you don't see effects -- really strong effects below .26 or .2, depending upon your interpretation, we thought based on the epi studies and the possibility that there was some effects, particularly really obvious clinical effects, in

epi studies, that dropping down to one-hour standard for the margin of safety was a prudent step. So it's never clear-cut as to which averaging times relate to which effects. So that's why we've incorporated that in our margins of safety.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: You know, I think it's safe to say that when you're studying in those epi studies, everybody's exposed to some level of NO2. So you have a chronic exposure. And imposed upon that you have these peaks on the bad air days. So whether the chronic exposure predisposes to the effects you measure with the time series studies is something of an open question. So that there is logic to trying to control those lower level chronic averages as well.

ADVISORY COMMITTEE MEMBER SHEPPARD: Yeah, I guess it's driven in part by the limitation of the epidemiologic studies because of the measurements that are done.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right.

ADVISORY COMMITTEE MEMBER DELFINO: I still think that there's a large body of evidence looking at acute exposure response relationships in the epidemiologic studies that clearly suggest the effects are below .18

ppm. So I mean I don't -- I would like to mirror what Dr. Sheppard said, and that's that, what is the basis for this .18 one-hour maximum standard? What is the scientific basis for it? I don't see it. I mean I don't see it emerge from this document.

And if you want a margin of safety, it's not just a margin of safety for the susceptible population based upon disease status, but it's also the susceptible population based upon exposure status. And that exposure status would be proximity to sources like traffic. And so if you have an ambient central site, you know, that, let's say, exceeds 100 ppb's, well, that's when you're going to see 160 to 180 near the freeway. You have evidence for this. It's all over the exposure section. It clearly shows that those -- those exceedances are, you know, 20, 40, 60, 80 percent higher close to the sources. So I think there needs to be some more clarity on this one-hour standard than there is.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: Well, I think it's safe to say we relied mostly on the chamber studies for the one hour, and less so on the epi studies.

ADVISORY COMMITTEE MEMBER DELFINO: Well, but we didn't do that with ozone, I don't think.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: We did --

ADVISORY COMMITTEE MEMBER DELFINO: I'm sure we didn't do that with ozone.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: We did to a large extent.

ADVISORY COMMITTEE MEMBER DELFINO: -- to a large extent.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah. I mean we used the 8-hour and the 1-hour studies -- the chamber studies really to drive a lot of that adding a margin of safety there. We did also contemplate a longer term average standard for ozone, which we ended up not recommending.

ADVISORY COMMITTEE MEMBER DELFINO: But the 70 Ppb's of ozone clearly is a level that you often see exceeded in the epidemiology studies. I mean I just did a -- we were at ATS -- a cut point at 70 ppb's for FEV1. And the association went down quite a bit when we just looked at, you know, up to 70 ppb's, suggesting 70 ppb's was not a bad choice, at least in that particular study.

But none of us are going to be able to do that at 180 of NO2. There's no threshold analysis that any of these epi studies will be able to do, with maybe some few exceptions. I don't know how high it goes in Europe, but it's just rarely -- we saw in the data it's just rarely

exceeded here. So there's no way of knowing whether the standard is protecting if we can't do some sort of threshold analysis, whether it's -- you know, there's a lot of ways of doing it, but...

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah. Well, as you know, the epi studies typically have gone from -- the early days when people did more quartile analysis and really divided up the data so you could really look at what kind of effects occurred over the different ranges. Now they've gone to more continuous exposure studies. So you don't see any real tests for nonlinearity. There's occasional tests in some of the studies where they look for interactions and so on, but no real tests of what the shape of the functional looks like. And it's quite possible that the functions would be linear anyway and you wouldn't see anything.

So we've typically used, as others have, the means of these studies as a best estimate for the effect levels. We say that the mean and above are likely -- you know, more likely to be driving those associations. And the lower end -- the uncertainties get a little greater as you go to the lower ends and the confidence intervals get wider as you deviate from the means.

So we've traditionally taken the means as effect

level. But there's a recognition that there's no clear bright line from those epi studies.

ADVISORY COMMITTEE MEMBER DELFINO: But the means that are in the table for the epidemiology section are all much lower than 180. All of them are much lower.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, those are 24-hour averages though.

ADVISORY COMMITTEE MEMBER DELFINO: What are 24-hour averages?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: In the table -- in the figure that I presented, those are 24-hour averages, not one-hour.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah. I guess one you have to kind of look and see, well -- and of course when we do our analysis you don't usually see a difference between 1-hour maximum, 8-hour maximum. And in fact with the study that I'm going to send you, the 24-hour average we did because the personal sampler was a 24-hour average sample.

So generally because -- from going from one day to the next you see this sort of general shift in concentration. You know, you're not going to see a difference in association. But then the question would be, from these studies -- remember, I asked for also maybe

adding the maximum. And here it's well -- so that way we could get some idea of they all have -- it's all hourly data, I believe. So -- and probably all of them -- I don't want to give you more work. Sorry. So I hate to do that. But we really need to know what the maximums are in these studies.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: A lot of them don't report the one hour. A lot of them are just 24 hour.

DR. KIM: Most of them are 24 hour.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Now, the Peel study, the number one study actually, I converted that to a 24-hour average. But that one did use a one-hour average, which was --

ADVISORY COMMITTEE MEMBER DELFINO: It would be easy to look at California data and just look at -- and just train your -- did we do that? Do they do that?

ADVISORY COMMITTEE MEMBER CHESTNUT: Well, here. But I mean where they talk about whether the 24-hour average versus the 1-hour max.

ADVISORY COMMITTEE MEMBER DELFINO: Okay.

ADVISORY COMMITTEE MEMBER CHESTNUT: Approximately four to six times. So --

ADVISORY COMMITTEE MEMBER DELFINO: Four to six times.

So all of that -- Okay. But, however, all of those -- all of those longer term averages are greater than .03 -- .03 and greater.

But we're really talking about 24 hour, not annual. So that's a different -- that's completely different than what's in here.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, we have the ratios for Los Angeles, for example, between 1 hour and 24. And it looks to be what, about --

DR. KIM: Yeah, the ratio for South Coast, say, is four. It looks like the ratio of -- at least as the annual average to 1 hour. I should have marked for you early. So that a -- say, an annual average 0.030 would translate to -- if the -- if the ratio of the 1-hour max to annual mean is about the same as the ratio of the 1-hour max to the annual -- excuse me. If the ratio of the 1-hour maximum to the annual mean -- it's indicated here at Table 1, A-47, the ratio for, say, South Coast for the 99th percentile is 4. If the 1-hour maximum to 24-hour average is about the same at 4, we are saying that --

ADVISORY COMMITTEE MEMBER DELFINO: I know it's not. I know from -- I've looked at your data for years and years and years. It's --

DR. KIM: It's 2?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: One hour and 24 hours, 2.

DR. GREEN: It's 2.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: And in Europe it's about 1.6.

ADVISORY COMMITTEE MEMBER DELFINO: Okay. So that means that in this table if you have an association at 20 ppb's, 24 hour, 30 ppb's, then you're really looking at maxima of 60 or 50, not 180. That's my point. So it has nothing to do with annual average. It's the daily day-to-day changes in NO2.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: That's a single -- the single highest 24-hour average. We've been taking the mean of all the 24-hour averages, you know, in the study to get the mean concentration of a long-term study or of a daily time series study.

DR. GREEN: Yeah, there's a difference.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: So one is the highest 24-hour average in the whole study and the other is the mean of all the 24-hour averages to get --

ADVISORY COMMITTEE MEMBER DELFINO: Right. But you could just translate that into the mean of the 1-hour

maxes.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: You could go all sorts of ways, yeah.

ADVISORY COMMITTEE MEMBER DELFINO: But I mean if it's still two times, then the mean of 1-hour max is going to be the same as the day-to-day changes. So I mean -- right? If you have -- if the mean of the 24 hours is 30 and the 1-hour maxes are generally two times the 24-hour average, then the mean of the 1 hours are going to be 60.

DR. GREEN: No, because it's on a day-by-day basis. The mean of the -- the 1 hour on a day-by-day basis is about twice the 24 hour. But if you take over the average -- but if you average it over the whole year, the 24 hour, then that's about four times less than the 1 hour.

ADVISORY COMMITTEE MEMBER CHESTNUT: Than the highest hour of the year.

DR. GREEN: Right, than the highest hour of the year.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, but we're talking about a day-to-day. Either it's time series or panel study. You're look at day-to-day concentrations. Let's say, you know, you follow your panel for, you know, 60 days, or it's a time series study of a year. You know, the question would be what is the corollary to that

24-hour average, you know, in the study? And if you're looking at an annual average, that's a little a bit different than, let's say, you're looking at a panel study done in a peak air pollution season.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right. And then for that you have to correct for the difference between your study period and the year. So if you're taking a high NO2 time, then you have to adjust for the fact we're talking annual averages. And vice versa, if you took it during the low of a two time, you'd adjust to get the annual average. So that's a factor as well when you're doing a two or three month panel study and converting that to an annual average. So we didn't base a lot on the annual average partially -- on the panel studies partially because some of the studies reported 1 hour, some 8 hour years, some were 24 hour. But most of them were part of the years, you know, they're anywhere from two weeks to three months.

We tended to rely more on studies that I've talked about --

ADVISORY COMMITTEE MEMBER DELFINO: But we know the time series studies, you know, are probably to a large extent driven by peaks. NO2 more than likely peaks during rush hour or sometime during the day, right? Because it's a daily time series. And so whether you use the 24-hour

average or the 1 or 8-hour maximum more than likely won't make any difference. I think -- there's a few studies that have done that and not really seen, you know, much of a difference.

So if you look at that, if you look at what is the average of the maximum in those studies, are you going to see 180? There's no way, because they don't even reach that on any day.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right. But that's a big presumption that these studies are driven by the 1 hour, right? Because if truly they were driven by 1 hour, I think you'd see much stronger effects in the 1-hour chamber studies. If you're seeing hospitalization, you'd see more than these -- you'd see some symptoms. You would --

ADVISORY COMMITTEE MEMBER SHEPPARD: Well, Bart, but that depends on the assumption that the effects of NO2 are just based on pure -- or NO2 in clean air. But if NO2 in polluted air is driving health effects, then you're going to see much bigger effects in the epidemiologic studies than you what would in a chamber study.

ADVISORY COMMITTEE MEMBER DELFINO: I think it's a matter of precipitation, that, you know, in -- in a background of relatively high exposures you have a peak, it's going to precipitate an adverse event leading to

hospital emissions or mortality.

DR. GREEN: But then why would you see more -- higher effect estimates for like a three-day lag or a cumulative -- I would think if you've seen more effects for like a three-day moving average or a three-day cumulative lag, then that would indicate it's not a 1-hour peak. Otherwise you'd see same day --

ADVISORY COMMITTEE MEMBER SHEPPARD: But that actually could be stochastic effects of repeated 1-hour peaks. So, you know, any given individual's more likely to be exposed to one of those peaks -- if you have multiple peaks over a period of three days, then any given individual's more likely to have been exposed to one of them than if you only had one peak over that whole three-day period. So still could be -- the biological effect still could be driven by peak exposures.

ADVISORY COMMITTEE MEMBER DELFINO: That's right. And especially for asthma, there's -- you still have to factor in the early and late phase kind of model and then, you know, acute inflammation, acute broncho-constriction and sort of smoldering inflammation. And we -- when we send you the paper -- we did an hourly distributed lag on on PM -- it's not NO2, because we didn't have hourly personal NO2 -- and found, you know, an effect on E and O in the last five hours of exposure, and that distributed

lag went down to zero. But we also found an accumulative multi-day moving average of PM had a similar effect on E and O.

So, you know, other people have done the same sort of thing, and including Jane Koenig in Washington, where you'd have this immediate acute impact on asthma and then more of a cumulative impact on asthma. And whether that's a different inflammatory processes or what; but using E and O, one would have to postulate it is a different impact on inflammation in the airways.

So I don't know, I still think --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: This is really interesting, because for NO2 there was a much bigger discrepancy or disconnect between the chamber studies and what you see in epi studies than there was for ozone. The concentrations were closer.

ADVISORY COMMITTEE MEMBER SHEPPARD: Right. Which suggests that ozone by itself causes a lot of the effects that are seen in epidemiologic studies. Whereas the evidence -- the clear implication is that NO2 by itself in clean air doesn't produce the same effects that you see from epidemiologic studies tracking with NO2 concentrations in polluted air. But that doesn't change -- I mean when you set a standard, the standard

actually isn't for the exposures that people are going to have in clean air and exposure chambers, right? It's the exposures that people are going to have in the real environment.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, that's why the PM 2.5 standard was really not interpretable when you look at, you know, chamber studies per se, because you have a certain mixture. And even caps is not the same as what people really breathe. So I think that has to be recognized, that you're really talking about the effects of a molecule versus what it represents.

ADVISORY COMMITTEE MEMBER CHESTNUT: But that also raises the possibility that the epidemiology studies that -- the NO2 is an indicator for a mix of pollutants that are -- that are the causative --

ADVISORY COMMITTEE MEMBER DELFINO: And it's a wonderful indicator. It's wonderful. I mean the Europeans figured this out way before we did, doing their cohort studies and all their other studies. They figured it out and they had some incredible results. They were very meaningful. And I think you said they actually regulate by proximity to source -- line sources like traffic and point sources, not just from one central -- no, am I wrong on that?

I think so.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: Well, they're thinking about incorporating -- I mean there is some discussion among you about changing their monitors and incorporating the -- moving away from only the central site monitors and try to incorporate more hot spots.

But let's have Francesco talk a little bit about that.

DR. FORASTIERE: Yeah, of course this of complex -- yes, Francesco Forastiere from Rome, Italy.

First addressing the point of the sites of the fix in monitors. There is discussion going on in Europe regarding the location of the monitors. The practice has been to monitor both the background -- urban background and also near the hot spots. So all the regression that we have in Europe do apply to both urban background and hot spots.

So the current standard that we have for Europe is .1 ppm for 1-hour maximum NO2. This is the current standard that has been going on since 1990.

We had a similar discussion in the formulation of the air quality guidelines for WHO last year, exactly the same discussion, whether NO2 should be considered a marker of traffic pollution or should be regulated by itself. And of course it's very difficult to arrive to a complete

answer.

The final decision from WHO was to have both 1-hour maximum air quality guidelines and also the annual standard. The 1-hour maximum was very much based on the clinical studies as we have here the evaluation. But those were a margin of safety was introduced there.

The air quality guidelines from WHO are guidelines, not standards. I mean just a suggestion for the governments for improving air quality. So that's why this precautionary principle was introduced. So that's why, instead of having .2 ppm, they decided for .1, actually 200 micrograms per cubic meter.

For the annual average the decision was 40 micrograms per cubic meter, which is .02, which was very much based on the long-term studies and also on the consideration that several short-term studies are showing an effect especially on respiratory conditions in asthma and hospitalization for those conditions.

Regarding the -- levels in Europe from the short-term studies, most of the studies in Europe have seen levels below the level we are discussing today, so below .18, although there are studies with higher values. And it's very difficult of course and it's very confusing to translate from one to another. And there is a ratio, as you have said, between 1-hour maximum and 24-hour

level. Most of the studies have been done for 24 hour instead for 1-hour maximum. But most of the studies have been seeing effects below .18.

CHAIRPERSON KLEINMAN: Can I ask you, Bart, to take a look at Table 5.7 on 5-45 of the TSD. This summarizes 1-hour indicator of population-weighted exposures.

So there is a series of distributions of upper and lower concentrations, and then the number of people affected within census tracks within those.

To what extent does this table help us, you know, solve this dilemma?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, technically, not at all because we don't use the actual concentrations that people are exposed to to determine what our standard should be. We try to base it based on the scientific evidence.

This could tell us the potential benefits of tightening to different levels and so on based on the current exposures. But we -- what's that? -- but, anyway, that's the short answer.

We could have a better idea of how much we should debate the issue if we knew that there was no difference between, you know, .2 -- or .1 and .2 or different -- I mean that would tell us how many people are impacted. And

EPA presented that, as you know, for the particle standard, actually tried to indicate what the relative risks were by going to different numbers. So that incorporated the number of people impacted at the different levels times the risk coefficients, you know, the slopes.

We basically do not use that information in our standard setting. We try to just go with what kind of effects -- what levels do we think effects are likely to occur, independent of the number of people who will be impacted.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: That's a real good point, because I think we've been pretty consistent with that through the PM and the ozone standards, is how we set standards and how we differ with EPA as well.

ADVISORY COMMITTEE MEMBER DELFINO: Ralph Delfino -- oh, sorry. Go ahead.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: Go ahead.

ADVISORY COMMITTEE MEMBER DELFINO: Well, then that brings up a good point. Looking at the California concentrations, there are epidemiologic studies in California that have been showing associations clearly below these -- below the level that you're proposing,

particularly the children's health study. So -- do you know what I'm saying? So basically you're saying that you're setting a level that's above any possible exceedance, while at the same time California-based studies are finding associations between current levels of NO2 and pediatric outcomes.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, not necessarily, if we go back to the slides here. The Gauderman studies, for example, if that's what you're referring to with the children's studies --

ADVISORY COMMITTEE MEMBER DELFINO: Yeah.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: I mean that's --

ADVISORY COMMITTEE MEMBER DELFINO: I guess that's looking back --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: -- study 7 and 8 on the table I put together. We said that the effect level -- the clear effect level -- I mean you can also debate where the effect level is. But the range of those upper studies are 25 to 38, with a mean of around 32. So both the 2005 and the 2004 Gauderman studies that show asthma onset as well as long-term change in lung development are in the low thirties. Because you could argue, you know, 25 to 38

from those with the mean in the low thirties.

ADVISORY COMMITTEE MEMBER SHEPPARD: Because then you're extrapolating to the annual standard from those numbers.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right. Those are long-term -- those were four or eight year average concentrations. So we go from -- those are long-term studies, so we're -- it's reasonable to take an annual average from those.

ADVISORY COMMITTEE MEMBER SHEPPARD: But then -- so effects were occurring with those being the average annual standards?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right.

ADVISORY COMMITTEE MEMBER SHEPPARD: So that suggests that if there's a relationship between any peak effects or any short-term effects and those measurable epidemiologic effects, then -- and it was in a period where the short-term standard's not being exceeded at all, it would suggest that the short-term -- or the new proposal for the short-term standard wouldn't necessarily protect against exposures that might be driving the effects that are seen in these epidemiologic studies.

ADVISORY COMMITTEE MEMBER DELFINO: Some of them are cumulative acute effects --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Right. And that's exactly why we --

ADVISORY COMMITTEE MEMBER DELFINO: -- exposed to some things like that. So --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: That's exactly why we're proposing an annual average, because we thought the one-hour standard -- even though it my drive down the whole distribution and prevent some of these effects, we couldn't guarantee it -- given the ratios of some of the counties, we couldn't guarantee that attaining even a .18 would guarantee low enough annual concentration.

ADVISORY COMMITTEE MEMBER DELFINO: So I guess my concern --

CHAIRPERSON KLEINMAN: I'd like to, you know, just interject. I don't want to squelch your discussion. But we've sort of jumped across our break and the recommendations and other issues. And I don't know about anybody else, but I think taking a break would be helpful, for me anyway.

So I'd like to, you know, suspend discussion, you know, at this point, unless there's something just has to be said right now.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Let me say one thing that I think this

has to be said so people can think about this during the ten-minute break.

Oh, Melanie too.

As I said during my presentation, if we absolutely knew that these were NO2-specific effects in these long-term studies, for sure I would add a margin of safety below these numbers, and I'd say, yeah, we got to drop below. But even in -- in these studies for sure, the childhood studies of Gauderman, it's very clear you could have the same figure that I had of the Gauderman slide and you could superimpose NO -- sorry -- PM2.5, EC and acid vapor and you see almost the same thing. So the correlations are, you know, .8 and you don't really know. And even in the panel's studies, Ralph's studies, my studies, others' studies, it's really impossible from those studies to say it's clearly NO2.

So that went into our thinking about this margin of safety and what kind of effects -- what kind of effect levels we should be concerned about.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: Having said that, Bart, I think I'll throw in something else too, that the statute actually requires us to set standards considering the interaction of multiple air pollutants. So that's another little twist that can get thrown into the discussion.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION
SUPERVISOR OSTRO: Interaction is different than --
(Laughter.)
OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION
SUPERVISOR OSTRO: Airing our laundry here.
(Laughter.)
OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION
SUPERVISOR OSTRO: Interactions are different than confounding.
OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION
MANAGER MARTY: Yes. Oh, yeah, yeah.
OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION
SUPERVISOR OSTRO: Okay. So if you have two pollutants that are exactly correlated, that's not an interaction; that's confounding by pollutants.
And epidemiologically -- again, Francesco can tell me if I'm right here. I haven't seen very many epi studies that have explicitly tested for interactions between NO2 and other pollutants in Europe. I did mention the Coscioni study where you show an effect modification of one versus the other. But that's not saying that the effects are multiplicative of the pollutant. So I don't know if you're aware of studies that have shown positively synergism between multiple pollutants in Europe.
DR. FORASTIERE: It's very difficult to test this

within a single study. The only way to approach is to have a multiple study, and you compare the coefficiency across the studies. That's the way the Coscioni paper and the method she adopted. And in that paper there was very clear increase of the PM10 effects when the NO2 levels were higher.

And it occurred to me that also the end-map study did not find exactly the same effect, although there was a suggestion of a similar phenomenon going on for U.S. So I think this is an answer -- a very difficult answer that could be responded only with multiple sites, not within a single place because of the correlation of the two pollutants.

CHAIRPERSON KLEINMAN: Okay. Let's reconvene in about ten minutes.

(Thereupon a recess was taken.)

CHAIRPERSON KLEINMAN: Okay. We were sort of in the middle of our discussion of the recommendations. And it seems to be apparent that there's a consensus -- although, you know, if there isn't, we'll figure this out in a minute -- but I think there was a consensus that the 250 ppb standard that currently exists does not allow sufficient margin of safety based on the epidemiology and the clinical studies.

What isn't really clear is the specific rationale

for the selection of the 180 part per billion proposed standard. And what I would like to put in as our advice to the staff is that the rationale and the method for coming -- you know, arriving at the 180 ppb standard be made more explicit in the document, that they provide more of a road map for how they got there.

And would that be okay for everybody in the room?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Could I add one thing --

CHAIRPERSON KLEINMAN: Yes.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: -- just to frame everything that took off before we had our break too, is just -- because I heard this thing on what are the standards -- what are they trying to regulate. And it -- because I heard -- the short-term 1-hour standard really has been aimed at NO2 as a molecule, not so much as a group of compounds. And I think that's the way OEHHA has made their recommendations of NO2 and that's why the strength of the support comes from the controlled human studies. The really advance that they've done now is with the annual standard, which is -- we really want to hear back on. It was more as a marker for a multiple number of compounds that -- because of what they've seen with epi studies and some of the weaknesses with it and some of the strengths with it as

well. And it seemed those things kind of get mixed up altogether.

CHAIRPERSON KLEINMAN: Yeah, I didn't hear any disagreement with the selection of the 30 part per billion annual standard. I thought, you know, the Committee felt that that was adequately described and the rationale for that is presented.

But there was some problem with the actual arrival at the specific proposed standard. I think that can be clarified, and that would be very helpful.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Okay. And we're also not asking the Committee to actually to give us the number of the standard. We're asking you to tell us whether it's supported, whether it -- we didn't go far enough or we went too far, all of that.

ADVISORY COMMITTEE MEMBER SHEPPARD: Well, I mean I might make the point a little stronger, because I heard points in the discussion that suggested not so much that their rationale wasn't made explicit in the document but that perhaps there wasn't a good rationale for not -- for setting this standard at 180 parts per billion; that perhaps the data suggest more stringent 1-hour standard would be more reasonable.

So it's not a matter necessarily just of

restating the rationale, because the -- unless there is some -- unless we can hear something about the argument. I mean if people verbally expressed a rationale that was convincing, then I might go along with that rather soft recommendation. But from the discussion I was hearing, it seems like the epidemiologic evidence supports a more stringent standard, because in my reading of the tables in the document and the description of the epidemiologic studies, the studies that looked at hospital admissions for asthma, ER visits for asthma, all were very likely occur -- these events were very likely occurring in response to peak concentrations that were below the -- 1-hour concentrations that were below the 180 parts per billion standard. And certainly those events wouldn't be very effectively dealt with by just an annual standard.

So I guess before I would be willing to just say, well, the document just needs rewriting, it would be important to hear what the -- that there actually is a good rationale for setting the standard -- for not setting the standard more stringently.

CHAIRPERSON KLEINMAN: Well, I think that could certainly be -- I accept that as an amendment. And we could, you know, ask for a more detailed margin of safety analysis to, you know -- and because there is a concern then, and I think it's been voiced by several members of

the Committee, that 180 may not offer enough margin of safety either.

ADVISORY COMMITTEE MEMBER SHEPPARD: That's what I was just saying. It --

CHAIRPERSON KLEINMAN: Yeah. So I think that's fine -- you know, I agree with that. And we'll --

ADVISORY COMMITTEE MEMBER SHEPPARD: I think maybe the difficulty comes in with the thought that the standard should be set based on just isolated NO2 as a pure -- as a gas all by itself in clean air. I mean maybe I'm just confused about what the intention of how the standards would be set would be. But I thought the idea of setting the standards was to try to optimally protect the health of a public who will be exposed to NO2 in the context of the air they breathe.

ADVISORY COMMITTEE MEMBER CHESTNUT: I'd like to just elaborate on that a little bit. I think it's -- the difficulty in -- or the hesitation about relying so much quantitatively on the epidemiology studies is that it's really hard to say with confidence that the causative agent in that association is the NO2. And we're setting standards here that says you have to lower the level of NO2 to this -- it has to be at this level.

Now, if everything that was associated with that -- I mean if you had to control traffic emissions,

you know, and using NO2 as a marker and you got the whole thing moved down, then I'd be more comfortable to say that, yeah, the quantitative results from the epidemiology studies are sufficient to imply a more stringent standard. But I don't think that's -- that's not necessarily what -- I mean maybe in effect that's what's going to happen. But I don't think that's what the setting of the standard on NO2 literally says.

So I think that's part of the difficulty, quagmire, quandary. What's the right word?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Can I respond to that?

It is a specific NO2 standard. But as Melanie indicated, if there is synergism -- and, as I said, I don't think there is evidence that I know of of synergistic effects at the levels we're talking about -- you're supposed to take that into account. So it is supposed to be a pure NO2 effect.

Now, I take into account what Laurie says, which is that we don't really know from the Epi studies what the averaging time is and what the pollutant is that's driving those things. We have some feeling that NO2 is playing a role, but we can't say too much more about it. So our reasoning for the 1 hour was that we're relying I think 95 percent on the clinical studies. Because, as in the case

of ozone, as I indicated in my presentation, we have very strong evidence on the actual dose, we have very strong evidence on what the effects are. And it's a very clean thing basing it on that pure scientific -- pure scientific results that we've observed.

We see effects in the allergen enhancement of .26 and we see more modest effects on the other -- on the airway responsiveness -- right? -- responsiveness, .2 to .3. Most of the studies at .2 show relatively mild effects. And some people have argued that those things shouldn't even be worried about. I also suggested that we see a little bit of a hint of an effect below .2. And, again others have argued that what you see is just normal variation and it shouldn't be worried about. We said we are going to worry about it a little bit.

So the clearest evidence is .26. It's consistent, it's robust, a lot of different endpoints. You see a little bit of something happening below that, maybe something at .2. We thought .18 was adding a sufficient margin of safety.

Now, I did say that we also threw in the epi studies. And that also goes into this margin of safety. Again, if these were only subclinical effects, you don't see any symptoms, nothing going on, maybe we wouldn't have added a margin of safety down to .18. Maybe we would have

been happy at .12 or -- I mean .20 or .22 or something. But we do -- so we do factor in the epi studies a little bit and qualitatively in that there could be this effect that we might be worried about.

But it's really -- we're trying to really draw this 1-hour standard based on the -- purely on the chamber studies for the most part, with support from the tox, that makes us believe that these things are happening and they're of concern and from the epi studies.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: Can I just clarify one thing?

The statute at least says interactions. So interactions could be synergism, but they don't need to be synergism. It could be actually antagonism. I don't think there's any evidence of it. It could be additive or it could be an effect modification. So it could be any of those things.

ADVISORY COMMITTEE MEMBER CHESTNUT: But I think that the concern is that it might not be NO2 at all that's causing that; it's the ultrafines, it's the carbon --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION MANAGER MARTY: Exactly. So how do you use the data in a quantitative way? Right, that's exactly the dilemma.

ADVISORY COMMITTEE MEMBER FANUCCHI: I have a question that's sort of related to that. It's about the

monitoring. So the monitoring is at a central site and that's not going to change. But we know --

MR. LARSEN: That's not --

ADVISORY COMMITTEE MEMBER FANUCCHI: No, that's not true?

MR. LARSEN: That's not true.

ADVISORY COMMITTEE MEMBER FANUCCHI: Okay. But not at a central -- I'm still having trouble with that, because I know the epidemiology studies that look at highways say that it's a lot higher at highways. So -- and they're not -- they're exceeding the 1-hour standard near a highway.

MR. LARSEN: I was having -- Larry Larsen. I was having this discussion at the break with a contrast.

Most, if not all, of our NO2 monitoring or NOx monitoring has been at site-specifically engineered placed away from the primary sources, because our primary emphasis on it was more like ozone control or things like that.

However, the monitoring very easily could change. So if there was an issue from a health perspective, a public protection perspective, we might very well see the monitoring network reconfigured to be more like our carbon monoxide measuring things, where for carbon monoxide we don't look at neighborhood scale sites away from the

roadways. We specifically seek out the worst carbon monoxide areas in a region at the most highly traveled intersections. Micro-scale, put the probes right at the roadway, and go after the worst case. And that's how you have to attain a standard.

So we could easily see a situation where you'd have to reach a .18 1-hour max right at the worst area for NO2 anywhere in your region.

ADVISORY COMMITTEE MEMBER DELFINO: Yeah, I think the -- I think that's a very reasonable approach to addressing this issue of the spatial variability of NO2 and what it represents. I mean you're right about CO. We have a station in Riverside on Magnolia --

MR. LARSEN: Exactly. That's --

ADVISORY COMMITTEE MEMBER DELFINO: -- that's exactly the one. And it's just much, much higher than everywhere else. And they do NO2 there too I think. And that was very informative.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: It goes both ways. Ostro here.

First of all, the first part of what you said was right. For most of the Epi studies that have gone on -- and by EPA regulations of siting, you cannot site it within a certain distance from roadways and you can't have it -- you know, there's height dimensions and there's

restrictions on what can be near it and so on and so forth.

So I'd say probably for all the U.S. studies the NO2 monitors are basically background monitors. Now, in Europe, having looked at some of these European studies -- and Francesco can verify it -- it's not the case. And some of the NO2 monitors are very close to roadways. Some are even on onramps or right next to onramps. So the siting criteria is much different in Europe.

So the first part of what you're saying is true. It is background monitors.

And for Ralph, I totally agree it would be great to monitor in these other areas. But you couldn't really use those same monitors for, say, time series studies on asthma hospitalization, because those monitors are only going to represent an area of about, you know, 500 meters or something like that -- under a kilometer -- because of the spatial aspects of NO2 dispersions. So that's the thinking of having background monitors.

Now, if you wanted to do special panel studies of people locating next to those monitors, it would be totally fine. Or if you just want to know how bad is bad. But for using them for epi studies you're going to run into problems with these time series.

ADVISORY COMMITTEE MEMBER DELFINO: But Actually

in Europe that is exactly what they're doing, where they're able to use the spatial distribution and data from spatially distributed monitors, to then model exposures at a variety of homes, not necessarily anywhere near those monitors. Am I correct on that?

DR. FORASTIERE: Yes.

ADVISORY COMMITTEE MEMBER DELFINO: There's an abundance of --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Yeah, that's what we're doing in here too, but those are more for more cross sectional and different types of studies, but not for -- You can't do those modelings for day after day for a time series studies. Those are really more useful for the cross-sectional prospective --

ADVISORY COMMITTEE MEMBER DELFINO: Well, that remains to be seen. I mean I think -- Jarrett was trying to do some of that I think with the land-use regression and moving -- moving the time series closer to the kind of model that we'd envisioned a long time ago and just couldn't figure out how to statistically do it, where you know where the participants live. That's an essential. If you know where the participants -- you know where the subjects who were admitted to hospitals or died lived, then you can model their exposure.

ADVISORY COMMITTEE MEMBER FANUCCHI: My concern wasn't so much for getting information for the epi studies. My concern was monitoring in a place that protects the health of the public. And so if we're deliberately moving ourselves away from where the NO2 is, is that really protecting the public?

ADVISORY COMMITTEE MEMBER PLATZKER: Well, one of the interesting aspects is, if you'd just look at another enhaled pollutant, environmental tobacco smoke, at least we can draw the subject's blood and urine and look for cotinine. So we know what the exposure is, but we really know what the individual exposure is like just based on a marker of inhaled cigarette smoke.

For NO2 we -- you know, with centralized monitoring we really don't know what the impact is on whatever the patient experiences. We're not doing serum NO2 or urine NO2. That's one of the basic problems in looking at health effects.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: And I think the good point that Larry Larsen made too is in the past the monitoring was done in a central site because it was looking at more regional pollutants and regional photochemical reactions. And now that, you know, our concern maybe -- actually is more regional levels NO2 are dropping. Now our concern seems to be more

micro scale. And that monitoring effort can be changed to focus on those aspects.

ADVISORY COMMITTEE MEMBER SHEPPARD: So I think we should draw some lessons from the small particle data set and standard setting that -- you know, I talked to some people about this during the break too. But it's a pretty similar situation, although epidemiologic's data are certainly more coherent and powerful for small particles. But really the chamber studies and epidemiologic studies don't fit very well. I mean the effects of the acute exposures of human volunteers to small particles don't show anywhere near the effects that you'd predict based on the epidemiologic studies. And yet standards have been set, and California was forward-looking in setting a standard that really was -- in that case it seemed to me was driven much more by epidemiologic evidence of health effects than by chamber study effects.

So, you know, I'd like to see some sort of balance I guess in this standard setting, or at least the -- you know, it seems like it's probably a similar situation where, with the particles you weren't -- in the chambers you were not -- people presumably aren't really reproducing what the exposures actually are in the real world. But if there are -- to whatever extent people

believe that NO2 might be driving the epidemiologic studies here, seems like a similar biologic explanation is likely that NO2 by itself isn't really sufficient at least in clean, filtered 50 percent humidity air to produce all the health effects that you see when NO2 is part of the mix in the pollutants that people are breathing.

And so I guess I would also feel more comfortable with the stringency of the standard if the standard included wording about where the monitoring would need to be. I don't know if that's possible. But, you know, having a standard that said that .18 parts per million NO shouldn't be exceeded for an hour at the hot spots or the places where you -- where you expect the highest concentrations to be would make me more comfortable.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: And we can do that. You can do that in the standard document what it's -- of the monitoring needs.

CHAIRPERSON KLEINMAN: Any other comments on this issue?

If not, Laurie had some additional comments on the staff report.

ADVISORY COMMITTEE MEMBER CHESTNUT: I just want to quibble about a couple little things. It's in the -- you know, there's a whole chapter on the vegetation effects. And I want to just speak to the welfare effects

for a moment.

And there's really not a problem in that chapter so much as what gets summarized back into the staff report. It makes it sound as though for visibility and for vegetative effects that this change to the standard doesn't necessarily do anything consequential. And I think that's not accurate. And I think that it's not necessary to say this isn't important. It may not be driving, you know, the proposed standards for this. But I think as a consequence of reducing NO2 emissions, you are going to get visibility improvements.

I'm not sure about the discoloration, if that's still an issue. I know we're at levels below this in Denver and we certainly still have discoloration, the brown color. But we clearly have -- it's a huge contribution to the particulate that's causing the visibility. So any reduction in it is going to be a visibility improvement.

And I think both in the chapter in the technical report and in the summary especially, it just talks about, well, there may not -- there's not any real foliar damage. But I think the question of the nitrogen deposition and the levels that you have, especially in the San Bernardino and Angeles National Forest and to some extent into the Sequoia, these are the highest levels in the country of

nitrogen deposition. I don't think we have -- we don't have well established what's the critical load that's tolerable, and maybe it is higher in the California mountains than in some places in the East where there's more humidity. But we're talking deposition levels at, you know, 10, 20 kilograms per hectare per year. And in the eastern part of the U.S. we're concerned at levels that are 5 to 10, that are -- you know, there's nitrogen saturation, it's causing impacts to the soils and the balances.

And so I just think it's not -- don't minimize that bringing down the two emissions is going to have ecosystem benefits that could be important, especially in the mountains surrounding the South Coast Basin.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: That's a good point.

DR. TEMPLE: Well, I wrote the chapter on vegetation. So if you have any more specific comments or questions about the vegetation chapter -- I'm sorry. Patrick Temple.

Is there a specific comment about the vegetation chapter or --

ADVISORY COMMITTEE MEMBER CHESTNUT: The detailed chapter itself, not so much. I think --

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF

BODE: It sounds like it's going to transfer those results to the --

ADVISORY COMMITTEE MEMBER CHESTNUT: But there's two short paragraphs in the staff report, one about visibility and one about the foliar injury. And I think that's where I'm most concerned, that they seem to imply that there's not much of a welfare benefit. And I think that that's -- its too narrow to just talk about -- it just focuses on discoloration and not so much the particle effect on visibility. And it just focuses on visible foliar injury versus the whole nitrogen deposition, acid -- acidification, runoff soil --

DR. TEMPLE: That was a much more complex question. And much of the nitrogen deposition comes from ammonia and other sources that are not NO2. And I think the specific focus here was on NO2. So there are multiple sources of nitrogen, and NO2 is only one of them.

ADVISORY COMMITTEE MEMBER CHESTNUT: Sure, sure. But it's a big one, especially in southern California I think on the --

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Also concerned that the stuff that was in the actual chapter didn't get transferred in the staff report, those points, which we can add.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

SUPERVISOR OSTRO: Which I think we could definitely remedy.

But I think another relevant question that you asked, and I'd like to know the answer as well, is would changes that we're talking about, going from, say, current levels to proposed levels, would we see noticeable differences in terms of visibility from those changes?

DR. TEMPLE: I have absolutely no knowledge about visibility. I'm a botanist. I can't help you there.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Does that answer your question?

ADVISORY COMMITTEE MEMBER CHESTNUT: Well, I think -- yeah, whether that -- well, whether this standard is going to mean any change to ambient air quality anywhere is -- you're already meeting this in most places. It's going to be a small increment in -- but that's a separate question from are you preventing increases from happening. So, yeah, the size of it may not be big in practice.

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: We'll check into that one too. That and the discoloration issue we'll talk to --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Our guy's not here who does that? Staff?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Yeah. The staff person who wrote that didn't come today.

CHAIRPERSON KLEINMAN: Okay. Any other comments or...

In that case, I think I'd like to thank everybody for their participation today. And we'll wrap up the proceedings and we will reconvene tomorrow morning at 8:30 where we'll start with the oral public comments.

Nine? We're getting a 9 signal.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION SUPERVISOR OSTRO: Well, I think since some people might just come tomorrow, I guess -- do we have to start at 8:30 tomorrow?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Well, I've got it in the agenda as 8:30. I mean it depends on --

ADVISORY COMMITTEE MEMBER SHEPPARD: Does the public expect us to start at 8:30?

ARB HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF BODE: Yeah, they're probably expecting 8:30. But if they got here early and -- depends if you guys want to start a little later, we could accommodate that. Just notify them --

CHAIRPERSON KLEINMAN: Well, I don't know about

the rest of the Committee. I would just as soon start at 8:30 and leave earlier if we get finished.

All right. Thank you very much. Good night.

(Thereupon the Air Resources Board, Air Quality Advisory Committee meeting recessed at 5:15 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Air Quality Advisory Committee meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 28th day of June, 2006.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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